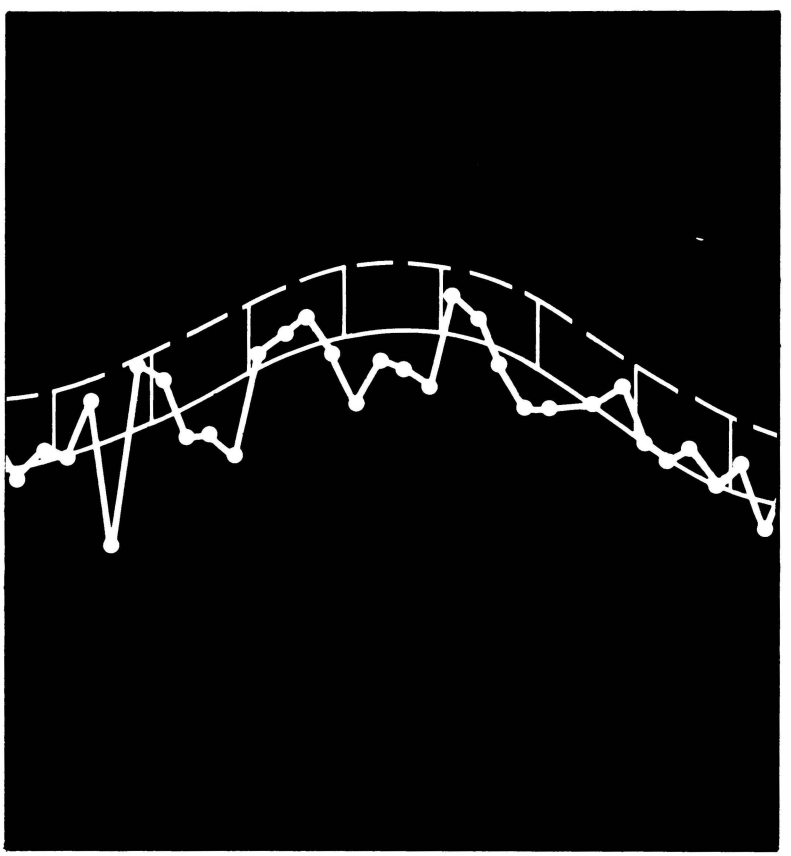
REPORT NO. 93
SUMMARY: AUGUST 1977 – MARCH 1979
Issued January 1983

CENTERS FOR DISEASE CONTROL

INFLUENZA

SURVEILLANCE



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES • Public Health Service

PREFACE

Summarized in this report is information received from State and local health departments and other pertinent sources, domestic and foreign. It is intended primarily for the use of those with responsibility for disease control activities. Anyone desiring to quote this report should contact the original investigator for confirmation and interpretation.

Contributions to the Surveillance Report are most welcome. Send them to:

Director, Division of Viral Diseases
Center for Infectious Diseases
Atlanta, Georgia 30333

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Issued January 1983

Centers for Disease Control	William H. Foege, M.D., Director
This report was prepared by:	
Center for Prevention Services	J. Michael Lane, M.D., Director
Immunization Division	Alan R. Hinman, M.D., Director
Surveillance, Investigations and Research Branch	Kenneth Bart, M.D., Chief
Surveillance and Investigations Section	Walter A. Orenstein, M.D., Acting Chief Timothy F. Nolan, M.D. Richard A. Goodman, M.D. Frank DeStefano, M.D. Edward W. Brink, M.D. Sandra Doster
Data Management Branch	Donald L. Eddins, Chief
Center for Infectious Diseases	Walter R. Dowdle, Director
Division of Viral Diseases	Gary R. Noble, M.D., Acting Director
Influenza Branch	Lawrence R. Schonberger, Chief Alan P. Kendal, Ph.D., Act. Asst. Dir. Med. Sci.
Epidemiology Program Office	Philip S. Brachman, M.D., Director
Consolidated Surveillance and Communications Activity	Stephen B. Thacker, M.D., Chief

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I. SUMMARY

A. 1977-1978 (August 1977-April 1978)

The 1977-1978 influenza season was unusual because of the reappearance of influenza A (H1N1) virus [reference strain USSR/90/77 (H1N1)] and the cocirculation of this virus subtype with influenza A (H3N2). This is the first recorded instance of failure of a pandemic strain to rapidly supplant and replace antecedent strains.

1. Influenza A (H3N2) Virus Activity (August 1977-March 1978). During August, an outbreak in the Marshall Islands occurred from which an A/Texas-like strain was isolated. In the continental United States, the first influenza A (H3N2) isolate was reported from Oregon in October, and reports of outbreaks (caused by A/Texas-like or A/Victoria-like strains) began in late November and continued until March 1978. Deaths from pneumonia and influenza, as reported in 121 cities, were increased for the 9-week period between January 7 and March 11, 1978.

2. Influenza A (H1N1) Activity (January 1978-April 1978). In May 1977 in China, and in November 1977 in the USSR and Hong Kong, influenza A strains whose antigenic properties were markedly different from other strains elsewhere in the world were isolated and identified as being of H1N1 subtype. Similar viruses were first isolated in the United States on January 15, 1978, from a high school outbreak in Cheyenne, Wyoming. By April 1978, 35 States had reported A/USSR-like isolates with, however, no apparent excess mortality attributable to this strain. The influenza A (H1N1) virus primarily affected individuals less than 25 years of age (i.e., persons born after 1952) who because previous influenza A (H1N1) viruses ceased to circulate in 1956/1957 had not been previously infected with influenza A (H1N1) virus strains. Attack rates as high as 75 percent occurred in some young adult populations living in dormitory-style accomodations.

3. Influenza B Activity. No reports of influenza B outbreaks were received during the 1977-1978 season. One State, Texas, reported influenza B/Hong Kong-like isolates from sporadic cases.

B. 1978-1979

1. Influenza A Activity (November 1978-March 1979). The first isolates were influenza A (H1N1) strains reported from areas bordering Mexico and the Gulf (Puerto Rico, Texas, and Southern California). Outbreaks of influenza A (H1N1) occurred subsequently throughout the United States, particularly among schoolchildren. The majority of the influenza A (H1N1) isolates exhibited a slight antigenic drift from the previous winter's influenza (H1N1) reference strain, A/USSR/90/77, and resembled virus detected in South America the previous winter, reference strain A/Brazil/11/78. Persons less than 26 years old (i.e., born after 1952) were primarily affected in a pattern similar to that noted with A/USSR-like viruses in the early 1978 outbreaks. Despite the widespread reports of illness, there were no excess reported deaths due to pneumonia and influenza. There were no confirmed influenza A (H3N2) isolates in the United States.

2. Reye Syndrome. A temporal association occurred between the epidemic of influenza A (H1N1) infection and an increase in reported cases of Reye syndrome.

3. Influenza B. A limited number of influenza B outbreaks occurred in nursing home residents through the spring after influenza A (H1N1) activity had subsided.

II. SURVEILLANCE METHODS

A. Mortality Surveillance

As part of its regular influenza surveillance system, the Centers for Disease Control (CDC) receives from 121 cities weekly reports of deaths due to pneumonia and influenza (P&I) and deaths due to all causes. The combined population in these cities is 70 million people, or 26 percent of the national total. A death is attributed to pneumonia if it appears on Part I(a) of the death certificate as the immediate cause of death or on the lowest used line of Part I as an underlying cause of death. A death is attributed to influenza if the word "influenza" appears anywhere in Part I or Part II of the certificate; if other causes

TABLE 1
Excess Mortality Due to Pneumonia and Influenza (P and I),*
United States, October 1957-February 1979

Period of Excess Mortality**	Population (1,000s)	Estimated Number of Excess Deaths Due to P and I	Rate of Excess P and I Deaths Per 100,000	Estimated Total Excess Deaths	Rate of Total Excess Deaths Per 100,000	Type of Influenza
Oct 1957-Mar 1958	173,232	18,500	10.7	69,800	40.3	A/(H2N2)
Mar - Apr 1959	176,420	1,400	0.8	7,900	4.5	A/(H2N2)
Jan - Mar 1960	179,323	12,700	7.1	38,000	21.2	A/(H2N2)
Jan - Mar 1962	185,890	3,500	1.9	17,100	9.2	B
Feb - Mar 1963	188,658	11,500	6.1	43,200	22.9	A/(H2N2)
Feb - Mar 1965	193,818	2,900	1.5	14,900	7.7	A/(H2N2)
Feb - Apr 1966	195,875	3,700	1.9	15,900	8.1	A/(H2N2)
Jan - Feb 1968	199,846	9,000	4.5	23,800	11.9	A/(H2N2)
Dec 1968-Jan 1969	201,921	12,700	6.3	33,800	16.7	A/(H3N2)
Jan - Feb 1970	203,736	3,500	1.7	17,200	8.5	A/(H3N2)
Jan - Feb 1972	208,232	5,600	2.7	24,600	11.8	A/(H3N2)
Jan - Feb 1973	209,851	3,680	1.8	8,997	4.3	A/(H3N2)
Jan - Mar 1975***	213,121	5,638	2.6	15,244	7.2	A/(H3N2)
Feb - Apr 1976	214,659	10,641	5.0	26,087	12.2	A/(H3N2)
Jan - Feb 1978	218,059	6,888	3.2	32,318	14.8	A/(H3N2)

*Mortality data based on final National Center for Health Statistics data
**No excess mortality observed in 1961, 1964, 1967, 1971, 1974, 1977 and 1979
***Beginning in 1975, estimates of excess deaths were calculated using time series analysis. Previously, regression estimates were used.

of death are also named, influenza takes precedence. The weekly report is a count of death certificates by week of filing and may include some deaths which occurred in a preceding week. Since the number of delayed certificates usually increases during holiday periods, these periods are often marked by an initial decrease in reported deaths, followed by an increase when the delayed certificates are finally counted.

The expected mortality level is calculated by using weekly data for the previous 5-year period, omitting epidemic weeks, and fitting a regression model which consists of linear secular trends and sinusoidal seasonal components about a general mean value.[1] In Figure 1, the reported numbers of deaths are shown as data connected by line segments; the solid line is the expected number of deaths; and the broken line is the epidemic threshold (1.65 standard deviations above the expected number). An excess in reported deaths for 2 or more consecutive weeks during winter months suggests influenza activity of epidemiologic interest.

Nationwide provisional estimates of excess deaths associated with influenza are based on a 10 percent sample of U.S. deaths that are reported to the National Center for Health Statistics (NCHS) a few months after the influenza season. Final estimates are calculated from NCHS statistics that include all U.S. deaths and are usually available 2-3 years following the epidemic period (Table 1).

B. Morbidity Surveillance

Morbidity surveillance for both 1977-78 and 1978-79 had two components: (1) weekly mailed reports from selected sentinel sites with observations on influenza-related morbidity, and (2) weekly telephonic reports from State epidemiologists with estimates of influenza-like activity. Table 2 shows the type of sites involved in the mailed reporting

TABLE 2
National Influenza Morbidity
Surveillance Sites, 1977-1979

Site Type	Number of Reporting Sites (% Total)	
	1977-78	1978-79
County-based	175 (8.6%)	1411 (42.2%)
School	1022 (50.4%)	1057 (31.6%)
Hospital/Clinic	397 (19.6%)	433 (12.9%)
Physician	257 (12.7%)	290 (8.7%)
Industry	175 (8.7%)	154 (4.6%)
Total	2026 (100.0%)	3345 (100.0%)

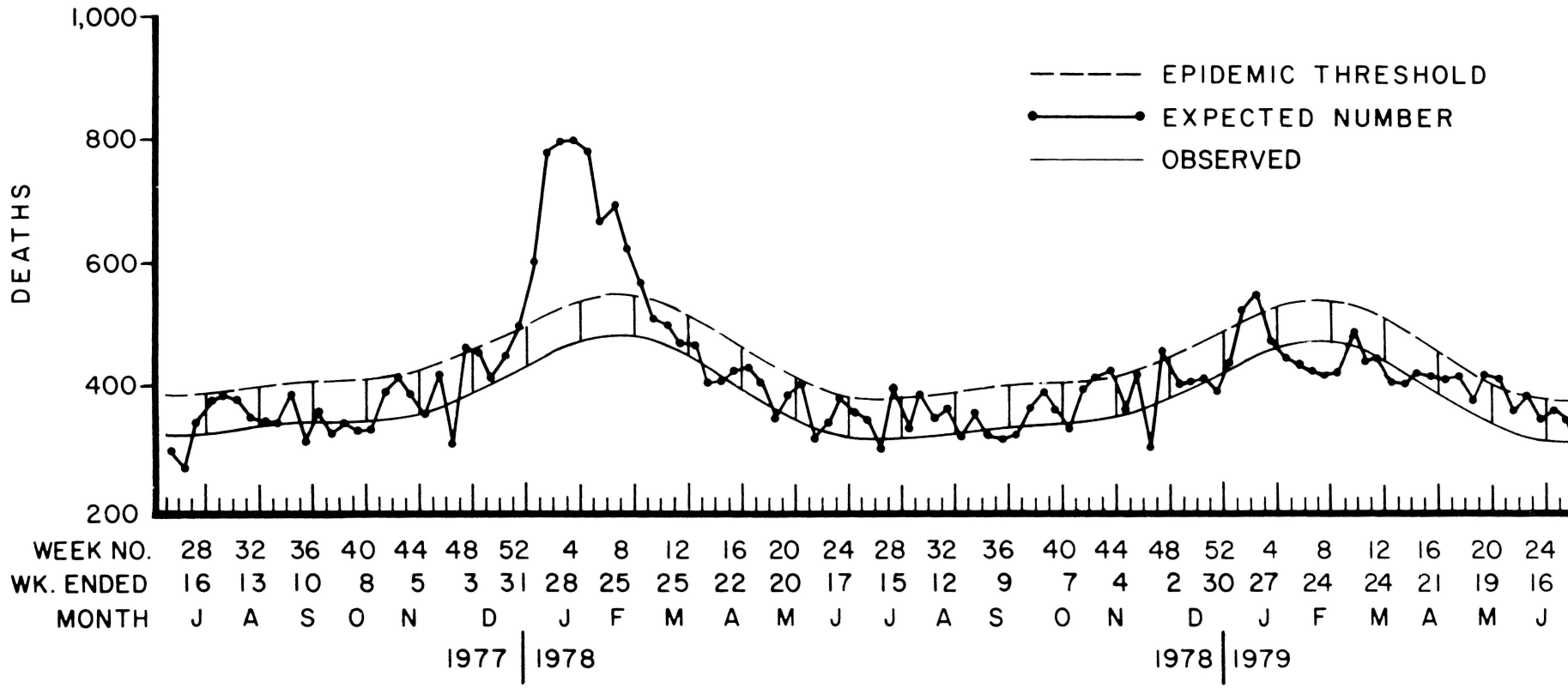
system. After the reports were received at CDC, they were entered into computer files. When informal reports of influenza-like activity were received, the computer files were searched for reporting sites in the vicinity and evaluated for signs of influenza-like activity. The use of such a system was somewhat hampered by the time lag involved in the mailing process and the inconsistent reporting of some sites.

The telephonic reporting consisted of weekly estimates of influenza-like activity by State epidemiologists or their designate. Activity was described as none, sporadic (isolated cases or outbreaks), regional (outbreaks occurring in counties with <50 percent of the State's population), or widespread (occurring in counties with ≥ 50 percent of the State's population). Epidemiologic and laboratory information on known outbreaks was included, if available.

C. Laboratory Reports

Beginning in September each year, about 60 World Health Organization (WHO) Collaborating Laboratories in State, city, and county health departments are asked to participate in surveillance by sending postcards each week to the WHO Collaborating Center for

Fig. 1 Observed and Expected Rates of Deaths Attributed to Pneumonia and Influenza in 121 United States Cities, July 1977-June 1979



Influenza (CCI) at CDC, reporting the number of specimens tested for virus isolation and the number of paired sera tested for rises in influenza antibody, together with the numbers of each type or subtype of influenza virus identified and the numbers of paired sera with significant antibody rises detected in the week of the report.

Included among the laboratories is the U.S. Air Force Diagnostic Virology Center at the USAF School of Aerospace Medicine, Brooks Air Force Base, Texas, which receives specimens from U.S. Air Force bases throughout the Nation and overseas and reports results of virus isolations to CDC.

The WHO CCI at CDC performs antigenic and, where appropriate, genetic analyses of representative influenza viruses submitted by laboratories throughout the Americas and elsewhere.

D. International Reports

The WHO Weekly Epidemiological Record and surveillance reports from many countries are monitored for information on reported influenza outbreaks throughout the world. The antigenic characteristics of viruses and the epidemiologic patterns experienced in other nations are used as a guide to anticipate the nature of influenza outbreaks in the United States.

E. Epidemic Investigations

CDC receives reports of investigations of selected outbreaks of influenza-like illness performed by State and local health personnel and academic researchers. Besides providing confirmation of influenza virus as the cause of an outbreak, the investigations provide explicit information on the epidemiology of influenza in outbreaks by documenting the signs and symptoms of the illness, the outbreak settings, vaccination status, age distributions, underlying illnesses, and the outcomes of influenza illness. When requested, CDC may provide laboratory and personnel support in outbreak investigations.

F. Quality of Data

All aspects of CDC's influenza surveillance are dependent on the voluntary provision of data. Because of the voluntary nature of data collection and the wide diversity to be found among submitters in availability of resources, an assessment of the overall quality of the collected data is difficult. During the influenza season, mortality, morbidity, and laboratory surveillance data are followed together. In our experience, the extent of influenza activity nationally is reflected by each surveillance component within any given period. Mortality surveillance provides consistent data for comparisons between years. Not all strains of influenza cause excess mortality, however. Laboratory surveillance alone can specify the exact type of virus and accurately indicate the onset of virus activity each season. Reports of virus isolation indicate the general spread of virus through the nation. Morbidity reports which have low specificity provide an indication of the extent of influenza-like activity in a defined region throughout an epidemic. All surveillance components are necessary at any one time to appreciate influenza activity.

When assessing a localized outbreak of suspected influenza disease, laboratory confirmation is desirable because the protean clinical respiratory presentation of influenza disease makes differentiation from other causes of upper respiratory illness difficult. Because influenza disease may present differently in age groups or among people with varying underlying illnesses or vaccination status, clinical case definitions have, of necessity, varied between outbreaks.

III. SURVEILLANCE RESULTS 1977-1978

A. Mortality Surveillance

Figure 1 shows P&I deaths for 121 reporting cities for July 1977 to June 1979. P&I deaths surpassed the epidemic threshold during the period of reported epidemic activity which began late December 1977 and ended in early March 1978. Throughout that period, reported P&I deaths were increased over the epidemic threshold in each of the nine geographic divisions used by the Department of Health and Human Services for disease reporting purposes.

For the nation, an estimated 6,888 excess P&I deaths and 32,318 total excess deaths occurred during the 1977-78 epidemic (Table 1).

B. Morbidity Surveillance

1. New England. Influenza A (H3N2) infections were confirmed by virus isolation in all six New England States, and influenza A (H1N1) infections were similarly confirmed in all but two States (Maine and New Hampshire). In early January, reports of widespread outbreaks of influenza affecting all ages were received from all States within this region except Massachusetts. In mid-February, an influenza A (H1N1) isolate was obtained from an outbreak among Wellesley College students, and reports of widespread influenza outbreaks were received from New Hampshire, Maine, Rhode Island, and Connecticut. Reported P&I deaths from cities within this region were only slightly elevated above the threshold value for weeks 2 and 4 of 1978.

2. East North Central. Illinois and Wisconsin reported sporadic influenza A (H3N2) isolates in late December. Reported deaths due to P&I from cities within this region were elevated above the epidemic threshold for 6 weeks beginning January 7, 1978. During this period, Illinois, Wisconsin, and Indiana reported widespread outbreaks. Eventually all five States had isolated influenza A (H3N2) viruses. Beginning in mid-February, four States--Ohio, Illinois, Michigan, and Wisconsin--isolated influenza A (H1N1) viruses from outbreaks affecting mainly colleges and military bases, along with some high schools.

3. West North Central. In this region, deaths due to P&I were only slightly elevated. Influenza A (H3N2) viruses were isolated by all seven States except South Dakota. Reports of outbreaks in military bases and colleges started in late February, and four States--Minnesota, Nebraska, North and South Dakota--isolated influenza A (H1N1) viruses.

4. South Atlantic. There was serological evidence of sporadic influenza A (H3N2) activity in Florida in early September. The first influenza A (H3N2) isolates were reported from North Carolina and Florida in late December. P&I mortality from selected cities was elevated for an 8-week period beginning January 7, 1978. By the end of the influenza season, all eight States and the District of Columbia had confirmed influenza A (H3N2) isolates.

Starting in mid-February, reports of widespread influenza outbreaks affecting colleges and military bases were received from the District of Columbia and five States--Maryland, Virginia, North Carolina, Georgia, and Florida. Influenza A (H1N1) viruses were isolated from six States.

5. East South Central. All four States in this region (Tennessee, Kentucky, Mississippi, Alabama) reported influenza A (H3N2) isolates, and P&I mortality from selected cities was elevated for 3 weeks beginning January 21, 1978. In mid-February, reports of influenza-like illness affecting young people were received from Kentucky, Tennessee, and Mississippi. In Nashville, influenza A (H1N1) isolates were obtained from students at Vanderbilt University, and reported absenteeism from high schools was increased. Kentucky was the only other State in this region to report an influenza A (H1N1) isolate.

6. West South Central. Although all four States within this region isolated influenza A (H3N2) viruses, few outbreaks were reported, and there were no periods of excess P&I mortality. Reports of influenza-like illness among students and armed services personnel began in mid-February and influenza A (H1N1) viruses were isolates in three States--Texas, Arkansas, and Louisiana.

In late February, San Antonio and Houston, Texas, reported sporadic influenza B isolates. These were the only reports of influenza B activity confirmed nationwide.

7. Middle Atlantic. Influenza A (H3N2) activity in New Jersey was confirmed by virus isolation in late November. By early January, all three States within this region reported widespread outbreaks and associated influenza A (H3N2) isolates. P&I mortality in 20 cities within this region was above the epidemic threshold for a 4-week period beginning January 7, 1978. Starting in mid-February, all three States reported outbreaks of influenza in high schools, colleges, and military bases. In New Jersey, approximately one-third of all college infirmaries reported increased visits to student health centers (SHC) for influenza-like illness. An outbreak at West Point Military Academy, West Point, New York, affected nearly 50 percent of the cadets. Influenza A (H1N1) viruses were isolated from outbreaks in all three States.

8. Mountain. In mid-November, Colorado reported the first sporadic influenza A (H3N2) isolates in this region. Although all eight States within the region had influenza A (H3N2) isolates, reported outbreaks were rare, and only minimal excess P&I mortality was reported. The first documented influenza A (H1N1) outbreak in the United States occurred in Cheyenne, Wyoming, during the week of January 15, 1978. Influenza A (H3N2) isolates were also isolated at this time. Influenza outbreaks with influenza A (H1N1) isolates were reported from Colorado, Utah, and Nevada. Six States in the region had influenza A (H1N1) isolates.

9. Pacific. In mid-November, Oregon reported the first influenza A (H3N2) isolate in the continental United States for the 1977-1978 influenza season, and subsequently all other States within this region had influenza A (H3N2) isolates. P&I mortality within the region was above the epidemic threshold for a 5-week period starting January 21, 1978. Influenza A (H1N1) isolates obtained in mid-February from college students in the San Francisco area were the first reported by California and influenza A (H1N1) isolates were reported also from Washington, Alaska, and Hawaii.

C. Laboratory Reports

1. Virus Isolation Reports. The extensive virus surveillance conducted by Collaborating Laboratories and others in 1977-1978, stimulated by interest in detecting influenza A (H1N1) viruses after their reported occurrence in Asia and the Soviet Union in 1977, resulted for the first time in the isolation of influenza viruses in each of the 50 States within one season.

Figure 2 illustrates the epidemic curve for influenza as judged by virus isolation results. Significant elevation in activity began in December, with influenza A (H3N2) viruses being isolated. The number of isolates increased rapidly in the last few weeks of 1977, and large numbers of influenza A (H3N2) isolates continued to be reported until the end of the epidemic, during late March 1978. Influenza A (H1N1) virus isolates in the United States were first reported in mid-January, and the number of isolates in February and March were approximately similar until late March when influenza A (H1N1) outbreaks were no longer reported. A very small number of influenza B viruses were isolated, and only in early March.

Overall reports of influenza A (H1N1) isolates were received from fewer States than reports of influenza A (H3N2) isolates; both subtypes circulated simultaneously in several regions (Table 3). In the Eastern regions, influenza A (H3N2) activity had often almost stopped when influenza A (H1N1) virus appeared, whereas in Western and Pacific regions, the viruses often cocirculated for several weeks.

To confirm the reported findings from morbidity surveillance that influenza A (H1N1) viruses predominantly infected children and young adults, who presumably had not been infected previously with related viruses circulating before 1957, an analysis was made of influenza isolation rates by age in several laboratories. This analysis showed that, although large numbers of specimens were collected from persons over 25 years old in the period when influenza A (H1N1) virus was prevalent, very few isolates were recovered from this age group (Table 4).

2. Antigenic Analysis. From the period October 1, 1977, to September 30, 1978, approximately 1,150 influenza isolates were submitted for antigenic analysis to the WHO CCI at CDC. Of these viruses, about 800 were from U.S. sources and 350 from foreign sources. The majority (76 percent) of influenza A (H3N2) viruses were similar to A/Texas/1/77 in hemagglutination-inhibition (HI) tests with ferret sera, the remainder being nearly all similar to A/Victoria/3/75. About 2 percent of the influenza A (H3N2) isolates were either similar to A/Brazil/53/76, in that they reacted equally well with both A/Texas/1/77 and A/Victoria/3/75, or exhibited low-level asymmetric antigenic drift away from A/Texas/1/77 (i.e., they were poorly inhibited by antisera to A/Texas/1/77, whereas antisera to the isolates reacted equivalently with A/Texas/1/77 and the other test isolates used in HI tests).

Influenza A (H1N1) viruses were initially found to be antigenically homogeneous and similar to influenza A (H1N1) viruses isolated in 1950-51.[2] Commencing with isolates recovered after February 1978, a slight variation in the H1N1 viruses was detected, and several variants were identified. The variant of greatest epidemiological significance was A/Brazil/11/78, isolated in May, which was representative of about 75 percent of H1N1 viruses submitted from South America. A small number of similar variants were detected among isolates in the United States, including viruses from New Jersey, Arizona, Washington, and Hawaii. Other variants (e.g., A/Arizona/14/78 and A/Lackland/3/78) did not appear to have any

FIG. 2 INFLUENZA VIRUS ISOLATIONS BY WHO COLLABORATING LABORATORIES IN THE USA, OCTOBER 1977 THROUGH MARCH 1978

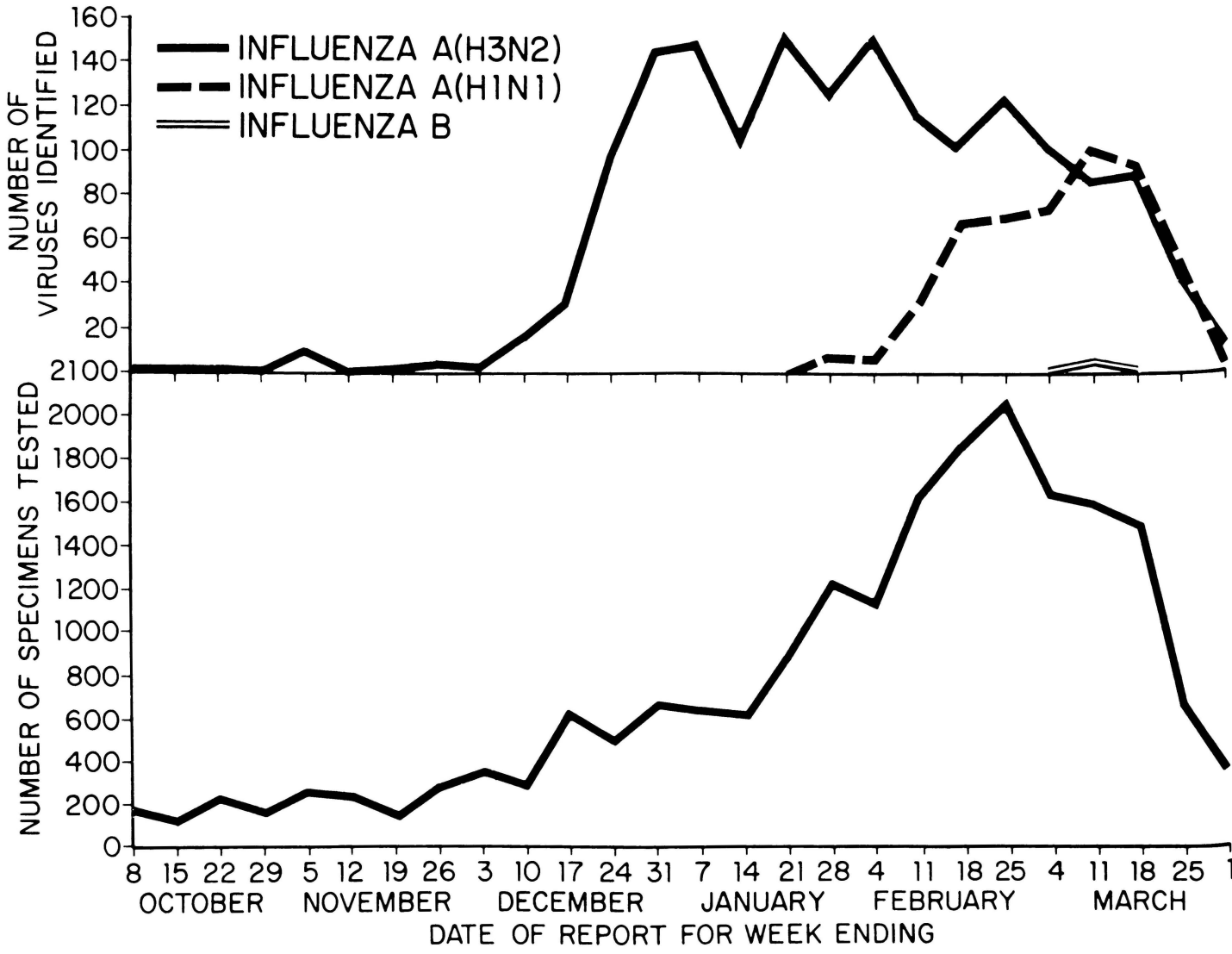


TABLE 3

Reported Isolations of Influenza A Viruses in the United States During the Winter of 1977-1978

	Isolation of Strains Confirmed as Resembling*:			Week Ending for Report of H1 and H3† in Same Week (Including USAF Bases)
	A/Victoria/3/75	A/Texas/1/77	A/USSR/90/77	
NEW ENGLAND				
Maine	X#	X	0#	
New Hampshire	0	X	0	
Vermont	0	X	X	March 4
Massachusetts	0	X	X	March 4
Rhode Island	0	X	X	
Connecticut	X	X	X	March 11
MIDDLE ATLANTIC				
New York	X	X	X	
New Jersey	X	X	X	
Pennsylvania	X	X	X	February 18
EAST NORTH CENTRAL				
Ohio	X	X	X	March 11
Indiana	0	X	0	
Illinois	X	X	X	February 18
Michigan	X	X	X	February 18
Wisconsin	X	X	X	March 4
WEST NORTH CENTRAL				
Minnesota	X	X	X	
Iowa	X	X	0	
Missouri	X	X	0	
North Dakota	0	X	X	February 18
South Dakota	0	0	X	
Nebraska	0	X	X	
Kansas	0	X	0	
SOUTH ATLANTIC				
Delaware	0	X	X	February 18
Maryland	X	X	X	February 18
District of Columbia	0	X	0	
Virginia	X	X	X	
West Virginia	0	X	0	March 18
North Carolina	X	X	X	April 4
South Carolina	0	X	X	March 18
Georgia	X	X	X	February 25
Florida	X	X	0	
EAST SOUTH CENTRAL				
Kentucky	0	X	X	
Tennessee	X	X	X	March 11
Alabama	X	X	0	
Mississippi	X	X	0	March 25
WEST SOUTH CENTRAL				
Arkansas	0	X	X	
Louisiana	X	0	X	March 18
Oklahoma	X	0	0	
Texas	X	X	X	February 4
MOUNTAIN				
Montana	0	X	0	
Idaho	X	X	X	
Wyoming	X	X	X	January 28
Colorado	X	X	X	February 18
New Mexico	X	X	X	
Arizona	X	X	X	March 13
Utah	X	X	X	
Nevada	0	X	0	
PACIFIC				
Washington	X	X	X	
Oregon	0	X	0	
California	X	X	X	March 11
Alaska	X	X	X	March 31
Hawaii	X	X	X	March 4
Guam	0	0	0	
Puerto Rico	0	X	0	
Virgin Islands	0	0	0	
TOTAL LOCATIONS REPORTING:	33	49	36	

*Confirmation of strain of virus was done at the WHO Collaborating Center for Influenza, CDC, using ferret antisera.

†Date for week ending in which virus isolate was identified

#X = yes, 0 = no

TABLE 4
Influenza A Isolations by Six State and City Health Departments in the USA during 1977-1978 from Patients in Different Age Groups*

Age of patients (years)	In period Oct.1, 1977 to April 30, 1978† Specimens No.	H3N2 isolates No. (%)	In period Jan. 15, 1978 to April 30, 1978# Specimens No.	H1N1 isolates No. (%)
≤5	408	32 (7.8)	257	1 (0.4)
6-10	231	33 (14.3)	153	4 (2.6)
11-15	278	33 (11.9)	200	12 (6.0)
16-20	547	46 (8.4)	442	45 (10.2)
21-25	237	47 (19.8)	193	11 (5.7)
Subtotal for all ≤25	1701	191 (11.2)	1245	73 (5.9)
26-30	126	20 (15.9)	70	0
31-40	144	20 (13.9)	86	1 (1.2)
41-50	97	16 (16.5)	55	0
51-60	116	15 (12.9)	72	0
61-70	98	10 (10.2)	66	0
>70	153	31 (20.3)	79	1 (1.3)
Subtotal for all >25	734	112 (15.3)	428	2 (0.5)
Total	2435	303 (12.4)	1673	75 (4.5)

*Summary of results from WHO Collaborating Influenza Laboratories in Arizona, Connecticut, Maryland, Nebraska, Pittsburgh and Tennessee. Specimens were submitted for diagnosis of respiratory virus or influenza infections.
†Patients were considered at risk of H3N2 influenza infection throughout the entire winter.
#Patients were considered at risk of H1N1 influenza infection after January 14, which is the first date of proven H1N1 influenza infection in the USA during the winter of 1977-1978.

epidemiological significance. Another isolated variant, A/Lackland/7/78, was documented to be related to the virus prevalent in Peru in July 1978.[3,4]

3. Isolation of a Mixture of H3N2 and H1N1 Viruses from a Single Person. During the course of an outbreak of influenza in a Cheyenne, Wyoming, high school at a time when both influenza A (H3N2) and influenza A (H1N1) viruses were prevalent in the region, one isolate was obtained that proved to be a mixture of A/Victoria/3/75-like (H3N2) and A/USSR/77-like (H1N1) viruses.[5] Reports of similar findings were subsequently received from Japan and the United Kingdom, suggesting that the mixed infection described in Wyoming was not a unique event. Such infections could provide a source of recombinant human influenza viruses deriving some genes from influenza A (H3N2) and some from influenza A (H1N1) strains.

4. Serologic Studies of Influenza A (H1N1) Virus Infections. Following the appearance of A/USSR/77-like virus in the United States in January 1978, it was apparent that not all infected individuals demonstrated rising influenza antibody titers using standard HI procedures with whole virus (WV) in allantoic fluid and chicken red blood cells. However, as had been observed earlier, the use of ether-treated (ET) virus increased the sensitivity of the HI test. HI antibody titer rises were detected in 36 (90 percent) of 40 infected individuals when tested with ET antigen (A/USSR/90/77), in contrast to only 60 percent showing an antibody rise when WV was used as antigen.

The age-specific prevalence of HI antibody to reference strains is shown in Table 5; sera were collected in December 1977 before the recognized outbreaks of influenza A (H3N2) and A (H1N1) viruses in early 1978, and in May 1978 after these outbreaks.

TABLE 5

Prevalence of Antibody to Influenza A/USSR/77(H1N1) Ether-Treated Virus and A/Texas/1/77 (H3N2)Virus in Sera Collected from Patients Hospitalized in Atlanta in December 1977 or in May 1978

Age in Yrs. (Dec. '77)	Date Serum Collected	No. Tested	Cumulative % with HI Titer ≥10	≥20	≥40	≥80	≥160	GMT*
			A/USSR/77(H1N1) Ether-Treated Virus					
1-12	Dec. '77	53	13	2	--†	--	--	6
	May '78	33	39	27	15	6	3	9
13-23	Dec. '77	66	21	11	4	3	--	7
	May '78	55	47	33	16	11	4	11
24-33	Dec. '77	53	77	55	34	15	2	18
	May '78	46	80	63	46	20	6	24
34-50	Dec. '77	50	92	76	48	24	12	29
	May '78	54	89	63	24	13	--	18
51-62	Dec. '77	55	80	58	27	7	--	16
	May '78	49	77	43	10	2	--	12
63-80	Dec. '77	56	80	39	14	--	--	13
	May '78	53	57	32	9	--	--	10
			A/Texas/1/77(H3N2) Virus					
1-12	Dec. '77	53	43	24	11	2	1	9
	May '78	33	70	48	30	15	9	16
13-23	Dec. '77	66	73	27	6	1	--	10
	May '78	55	80	44	18	5	--	14
24-33	Dec. '77	53	58	36	4	2	--	10
	May '78	46	76	46	15	4	--	13
34-50	Dec. '77	50	62	20	2	--	--	9
	May '78	54	67	30	7	2	--	10
51-62	Dec. '77	55	64	33	2	2	2	9
	May '78	49	65	35	14	6	2	12
63-80	Dec. '77	56	61	30	11	4	--	10
	May '78	53	70	30	15	4	2	11
≥81	Dec. '77	24	79	42	21	17	8	16
	May '78	31	64	29	19	10	3	12

*Titers <10 assigned a value of 5 for calculation of geometric mean titer

†-- indicates zero

Chicken red blood cells used in HI test

The finding of A/USSR/90/77-specific antibody in sera collected from children in December 1977, before A/USSR/90/77-like virus outbreaks were detected in the United States, remains unexplained; but it is possible that low levels of infection with influenza A (H1N1) viruses occurred in the United States in 1977, a time when the virus had already been isolated in parts of Asia (see Section III.D). Comparison of HI antibody prevalence in sera collected i December and May suggests that about one quarter of the children and young adults susceptible t infection were infected with influenza A (H1N1) virus during the winter of 1977-78.

D. International Reports

Influenza outbreaks caused by the influenza A (H1N1) subtype were first recognized in China in May 1977, reaching a peak in that country in October. Similar strains of virus reportedly caused outbreaks in the Philippines during June and July, and from November 1977 to January 1978 outbreaks were recognized in the USSR, Hong Kong, Singapore, and Malaysia. Between December 1977 and February 1978, the A/USSR/90/77 (H1N1) virus was also isolated in Finland, eastern and western Europe, the United States, and Japan (Table 6). Illnesses were generally mild, although attack rates were often high in individuals born since the last circulation of related strains in 1957.

Influenza viruses of the subtype A (H3N2) were isolated together with influenza A (H1N1) in a number of countries, whereas in other countries only H3N2 strains were isolated. Both A/Victoria/3/75 influenza A (H3N2) and A/Texas/1/77 influenza A (H3N2) viruses were isolated in many areas, although A/Texas/1/77 later became the predominant strain. In some countries, excess mortality was reported in association with isolation of influenza A (H3N2) viruses.

Scattered isolates were reported of influenza B, antigenically similar to B/Hong Kong/5/72.

E. Epidemic Investigations

1. Influenza in Mercer County, New Jersey. During the 1977-1978 influenza season, two distinct influenza epidemics occurred in Mercer County, New Jersey. The first epidemic began and peaked in December and was due to influenza A (H3N2) strains. Widespread illness due to the influenza A (H1N1) pandemic strain began in February. The occurrence of these two distinct outbreaks in Mercer County provided an opportunity to study, retrospectively, the communitywide impact of each strain.

Data were collected on virus isolations and nonvirologic indices of influenza activity for the 15-week period which spanned both outbreaks from November 27, 1977, to March 11, 1978. Data on influenza isolates were obtained from the Virology Laboratory of the New Jersey Department of Health. Nonvirologic indices of influenza-like activity were (1) emergency room (ER) visits and hospital admissions for acute respiratory disease (ARD) at three of five area hospitals, (2) the weekly rate of absenteeism for 6 of 95 county public schools, (3) the rates of infirmary admissions due to influenza at two colleges and one boarding school, (4) employee absenteeism at a large Mercer County employer, and (5) the rate of febrile illness among 424 residents of four community nursing homes.

Figure 3 shows a comparison of the virus isolations and nonvirologic parameters studied during the two outbreaks. The State Department of Health tested 1,152 pharyngeal washings during the period of the study: 132 were positive for influenza A (H3N2) strains and 16 were positive for the influenza A (H1N1) strain. Influenza A (H3N2) viruses were isolated from patients ranging in age from 2 to 90 years, but the oldest person from whom an influenza A (H1N1) strain was isolated was 23 years old.

Christmas vacation and the occurrence of several snowstorms probably had the major affect on school attendance. Work absenteeism showed no consistent trends. Both the influenza A (H3N2) and the influenza A (H1N1) outbreaks were associated with increased ER visits, but increased hospital admissions occurred only with the influenza A (H3N2) outbreak. This increase occurred within 2 weeks of the onset of the influenza A (H3N2) epidemic, and P&I deaths rose from 10 to 28 per week.[6]

2. University of Colorado, Boulder. During the week ending February 10, 1978, the Student Health Service (SHS) at the University of Colorado reported a sharp increase in the number of students seen with an influenza-like illness. An epidemic investigation was conducted during the week of February 27 to define further the university-associated outbreak and to determine whether the surrounding community of Boulder had been affected.

Enrollment at the university was approximately 22,000; faculty and staff

TABLE 6

Isolations of Influenza Viruses Worldwide, by Month of First Report, October 1977--September 1978*

Month of First Report	Virus Type (Subtype)		
	A(H3N2)	A(H1N1)†	B
October 1977	Jamaica United States		
November	Canada Israel Japan USSR	Hong Kong Singapore Taiwan USSR	Taiwan
December	China Korea Morocco Netherlands Portugal Switzerland Taiwan	Czechoslovakia Japan	
January 1978	Austria Egypt Finland France Germany, E. Germany, W. Hong Kong Hungary Indonesia Iran Ireland Italy Malta Norway Pakistan Poland Sweden Turkey United Kingdom Yugoslavia	Belgium Bulgaria Finland Germany, E. Germany, W. Hungary Indonesia Iran Malaysia Poland Rumania United Kingdom United States Yugoslavia	
February	Brazil Denmark French Guyana Senegal South Africa Spain Uganda USSR	France Greece India Israel italy Netherlands Norway	France Germany, W.
March	Denmark Turkey	Australia Canada Panama Sweden	United Kingdom United States
April	Argentina Brazil	Argentina Fiji France	
May	Ecuador	Brazil Chile	
June		Hong Kong#	Australia
July		New Zealand	
August			Canada§
September		Australia#	United States#

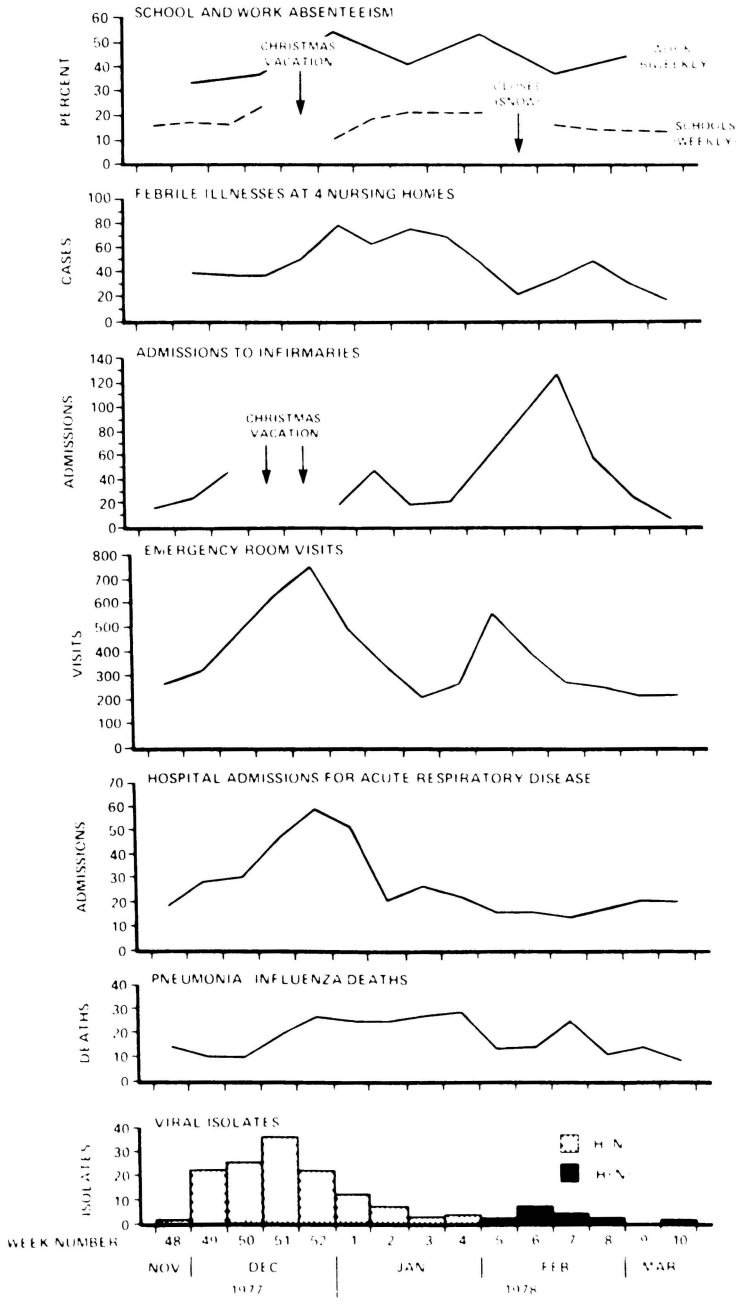
*From Weekly Epidemiological Record in 1977, 1978 and other reports to the WHO Collaborating Centers, Atlanta and London

†First identified in China in May 1977, and in June in the Philippines

#Second appearance in this 12-month period

§Imported case

FIG. 3 CORRELATION OF THE NONVIROLOGIC INDEXES OF EPIDEMIC INFLUENZA IN MERCER COUNTY, N.J., WITH THE NUMBER OF ISOLATES OF H_3N_2 AND H_1N_1 IN THE STATE, BY WEEK, NOVEMBER 27, 1977 – MARCH 11, 1978



numbered 1,800. The combined population of Boulder and the University was about 80,000. The investigation included a review of SHS records, a questionnaire survey of one dormitory (1,100 residents), a telephone poll of 156 randomly chosen faculty and staff, a poll of community physicians, tabulation of hospital discharge and emergency room records, contact with three nursing homes, and the collection of virus cultures and sera from 10 acutely ill students and 15 community residents. For the university investigation, a case of influenza was defined as onset of illness after February 1 consisting of at least three of four symptoms (fever and/or chills, muscle aches, headache, and cough).

Seven hundred and seven (64 percent) students (mean age 19.3 years) living in the dormitory completed questionnaires. The attack rate was 37.5 percent and the mean temperature (of 119 students) was 101.5°; 74 percent of the students missed an average of 2.8 days of school and 178 (25 percent) sought medical care. One hundred twenty-two of the faculty and staff were contacted. The attack rate was 9.1 percent, and the mean age of those ill was 41.8 years. At the SHS, visits for influenza-like illness first increased during the week ending February 3 and peaked during the week ending February 24; monthly totals for ARD diagnoses clearly indicated an increase for such visits during February 1978. Five of 10 cultures taken from acutely ill students yielded influenza A (H1N1) isolates.

Communicable diseases reporting for cases of influenza-like illness to the Boulder City-County Health Department correlated with the increases seen at the SHS. Four pediatricians and eight family practitioners who were polled by telephone observed an increase of influenza-like illness involving younger age groups. ER visits and hospital pediatric discharges for ARD did not increase. School absenteeism records did not reflect a significant increase in absenteeism. Of the three nursing home facilities contacted, none reported outbreaks of influenza. Only one of 15 virus cultures obtained from persons in the community yielded an influenza A isolate; this was an H3N2 virus from a 30-year-old man. (Reported by Theodore Eickhoff, M.D., University of Colorado, and Martin Seigel, M.D., Influenza Task Force, CDC.)

3. Ann Arbor, Michigan. In mid-January 1978, an influenza A (H1N1) virus was isolated from an individual in the Ann Arbor, Michigan, area. Shortly thereafter, influenza-like illness was noted among students at the University of Michigan, Ann Arbor. An investigation was conducted to determine the extent of the outbreak among university students and staff and in the surrounding community.

Questionnaires were administered to 600 students, faculty, and staff who were chosen randomly from the university directory. Fifty-five (14 percent) of 381 persons returning the questionnaire had experienced onset of an influenza-like illness (defined as cough plus fever or chills and an additional symptom: muscle aches, headache, sore throat, stuffy nose, or fatigue) in the period February 3-March 9. Symptoms included cough (100 percent), fever (89 percent), chills (80 percent), and fatigue (91 percent). Temperatures were recorded by 32 persons; the mean highest temperature was 101.5°. The mean number of days of confinement to bed was 3.8; 36 percent sought medical care. The attack rate among those living in dormitories, fraternities, or sororities was similar to that among those in noncommunal residences. The attack rate was 27 percent among persons <22 and 7 percent for persons $\geq$22 years ($p=0.001$). Similarly, the attack rate for all students (21 percent) was significantly greater than that for university faculty or staff (6 percent, $p=0.0001$). The number of cases of influenza-like illness seen at the SHS peaked during mid-February, although influenza A (H1N1) viruses were still isolated through March.

Ann Arbor is served by University Hospital and by a large community hospital. Visits to the adult and pediatric ER's and the walk-in medical clinic at the University Hospital remained constant during January-March. Pediatric medical admissions increased slightly when compared to 1977, while croup admissions during 1978 (20) were markedly increased when compared to 1977 (3). At the community hospital, ER visits and admissions for croup were unchanged. Absenteeism varied among three elementary schools and a junior and senior high school in the community. (Reported by Arnold Monto, M.D., University of Michigan School of Public Health, and Robert A. Gunn, M.D., Influenza Task Force, CDC.)

4. Marquette University, Milwaukee, Wisconsin. An epidemic of influenza A (H3N2) had occurred at this university in November 1977, and the attack rate in dormitories approached 25 percent. On Monday, February 13, 1978, about 200 students visited the Marquette SHS with an influenza-like illness; this was more than twice the daily average of all students attending the clinic. This excess of visits to the SHS continued unabated throughout the week of February 13.

Three groups within the university community were surveyed by questionnaire to define the epidemiology of the outbreak: (1) the 733 residents of one coeducational undergraduate dormiory (mean age 19.2 years; range 18-47); (2) the 267 junior and senior dental students (mean age 25.0 years; range 23-40); and (3) the 715 university faculty members (mean age 41.1 years; range 19-72). The three groups were chosen because virtually all their members would have been exposed to the A/USSR strain.

The overall response rate to the questionnaire was 76 percent. Attack rates varied markedly by age with highest rates in those under 22 years of age (61.5 percent), intermediate rates in those 23-26 years old (18.6 percent), and the lowest rates in people older than 27 (9.0 percent). The overall attack rate in those surveyed was 35.9 percent.

Another survey finding was that a history of A/New Jersey/76 (Hsw1N1) vaccination in 1976 did not affect the risk of illness in this influenza outbreak. This finding is consistent with that of a study of A/USSR/77 (H1N1) antibody responses following A/New Jersey/76 vaccination in 1976, which demonstrated little heterologous A/USSR/77 antibody response in the 19- to 23-year-old age group.[7]

5. United States Air Force (USAF) Influenza Immunization and Surveillance Program. The USAF Influenza Immunization and Surveillance Program was initiated in the fall of 1976 and became a year-round surveillance effort in the summer of 1978. The program, directed by the Epidemiology Division of the School of Aerospace Medicine, Brooks Air Force Base, Texas, is an Air Force-wide effort consisting of influenza surveillance at 23 sentinel bases and 105 nonsentinel bases. Each sentinel base submits weekly influenza-like illness rates and appropriate specimens for virus isolation or serologic evaluation. Specimens are collected on a monthly basis from patients 10 years of age or older with clinical respiratory disease of less than 2 days duration. Nonsentinel bases report rates of influenza-like illness when they exceed 5 cases/1000/week. They are encouraged to submit specimens for virus isolation to State or Federal laboratories whenever the threshold rate is exceeded.

a. Royal Air Force Base (RAF) at Upper Heyford, England. The first outbreak of influenza A (H1N1) in a U.S. military population occurred during the first week of January 1978 at the RAF Base at Upper Heyford, England. Between January 7 and February 5, an estimated 580 clinical cases of respiratory illness were attributed to influenza A (H1N1). The epidemic reached a peak during the first 7 days of the outbreak and clinical illnesses were noted primarily among 17- to 24-year-old active duty airmen. Of the 37 cases confirmed by isolation of A/USSR/90/77-like influenza virus, 34 were young airmen and three were wives of airmen. Very few cases occurred in the schoolage dependent population. A seroepidemiologic survey of military personnel who did not experience respiratory illness during the outbreak showed that the prevalence of HI antibody titer $\geq$1:8 to A/USSR/90/77 virus was 13 percent for $\leq$24-year-old personnel, 63 percent for the 25- to 29-year-old personnel, and 95 percent in $\geq$30-year-old personnel. (Reported by Epidemiology Division, School of Aerospace Medicine, Brooks Air Force Base, Texas.)

b. United States Air Force Academy, Colorado. During the period January 30 to February 5, 1978, 74.5 percent of the 4,316 member cadet wing reported an influenza-like illness. Cadets range in age from 17-26 years. There was no significant difference noted in the proportion of ill cadets in the 17-20, 21-24, or 25-26 age groups. Influenza isolates collected from ill cadets in mid-January just prior to the outbreak were identified as being influenza A (H3N2) strains. However, throat washings collected from 35 ill recruits during the outbreak yielded isolates of influenza A (H1N1). (Reported by Epidemiology Division, School of Aerospace Medicine, Brooks Air Force Base, Texas.)

c. Air Force Military Training Center, Lackland Air Force Base, Texas. On February 7, 1978, the incidence rate of upper respiratory illness (URI) among basic trainees exceeded a pre-established training center-specific epidemic threshold rate of 20 cases/1000/week. Between February 7 and March 20, an estimated 1,961 URI cases occurred among trainees at the center. During the peak period of the outbreak, February 7-13, 507 cases were observed. The number of cases declined over the next 4 weeks. This gradual return to endemic levels has been characteristic of past influenza outbreaks at the training center, where there is a continuous introduction of susceptible new trainees. Throat washings collected prior to the outbreak indicated influenza A (H3N2), while during the outbreak, influenza A (H1N1) predominated. Evidence gathered through seroepidemiologic studies of various 50-man flights suggested that flights newly formed during the last week of January and in February were

heavily seeded by trainees with a URI, and that the outbreak slowly spread to other flights formed earlier. (Reported by Epidemiology Division, School of Aerospace Medicine, Brooks Air Force Base, Texas.)

IV. SURVEILLANCE RESULTS 1978-1979

A. Mortality Surveillance

Figure 1 shows that deaths due to P&I exceeded threshold levels during the 3-week period ending January 20, 1979. This period preceded the period of major virus activity demonstrated by virus isolations (Figure 5), and the P&I elevation may have been related to delayed reporting after the Christmas and New Year holidays. The 1978-1979 influenza season differed from many previous years in that although outbreaks of influenza occurred throughout the country, no increased P&I-associated mortality resulted. Outbreaks generally involved persons less than 26 years old and the elderly, among whom increased mortality is usually observed, were spared.

B. Morbidity Surveillance

During the winter of 1978-79, most reported sporadic cases and outbreaks in the United States were attributed to influenza A (H1N1)-like viruses. As noted in 1977-78, these viruses affected mainly persons born after 1952, who were unlikely to have had any prior exposure to the influenza A (H1N1) viruses that were replaced in 1957 by Asian influenza A (H2N2) virus. A limited number of cases and outbreaks were caused by influenza B viruses.

The first virus isolations were from sporadic cases in Texas and in October. Outbreaks first occurred in California and Texas in October and by December sporadic, and then widespread, outbreaks were reported throughout the western and southwestern regions of the United States. By late December, outbreaks had spread to the southeast region and, following the Christmas holiday, influenza outbreaks were reported in the northwest, the northeast, and the midwest regions. A few localized outbreaks of influenza B occurred later in the spring.

Figure 4 depicts the reported maximum extent of influenza morbidity reported by each State between December 1978 and March 1979.

1. New England. Reports of influenza were limited to focal outbreaks in this area. The first influenza A (H1N1) isolate in Vermont was obtained from a 13-year-old and reported in mid-January. A focal outbreak among students in New Hampshire occurred in late January, and by early February influenza A (H1N1) isolates had been reported in that State and in Connecticut. Influenza A (H1N1) isolates were also reported from Maine and Massachusetts.

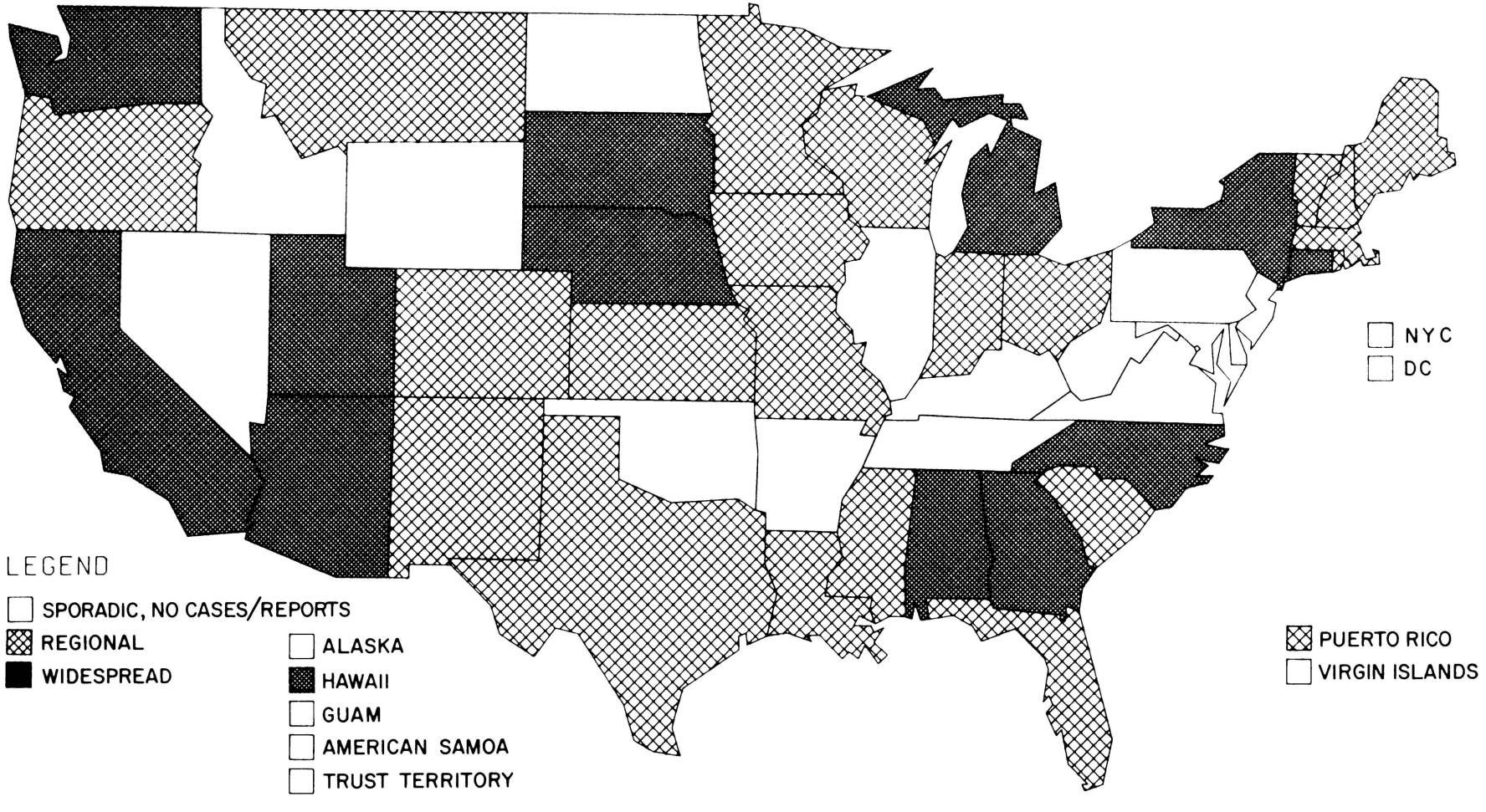
2. Mid-Atlantic. Sporadic cases and limited outbreaks occurred in this area. In New York City, the first influenza A (H1N1) isolate was recovered from a 73-year-old person who had experienced the onset of an upper respiratory infection on November 6. In New Jersey, an influenza A (H1N1) isolate was obtained from a 21-year-old military recruit who had become ill on December 11. By late January, outbreaks had been reported in New York City, and additional isolates had been obtained in New Jersey from sporadic cases among military personnel as well as from children in school-related outbreaks. The first confirmed outbreak of influenza in Pennsylvania was reported in mid-February (see Section E.4) and involved nursing students in Sayre, Pennsylvania.

3. East North Central. Influenza A (H1N1) and influenza B viruses were isolated from sporadic cases and outbreaks in this area. By late December, outbreaks and isolates of influenza A (H1N1) virus had been reported from Illinois. Influenza A outbreaks occurred in Wisconsin beginning in mid-January, and by the end of the month, isolates had been reported from Michigan. Ohio reported influenza A (H1N1) and B isolates.

The first outbreak in Wisconsin occurred on January 19 among students at Beloit College and among schoolchildren at an elementary school in Whitehall. Influenza A (H1N1) was documented in 31 of 72 counties. A total of 30 outbreaks was reported from Wisconsin. Twenty-five occurred in counties where influenza A or B had been documented during the season. Influenza A was confirmed by the laboratory in 10 of those outbreaks and influenza B in one. Seventy-seven of 78 (99 percent) of confirmed H1N1 cases occurred in persons less than 26 years old. Influenza B was documented in 13 counties, including an outbreak in a Vernon County school on March 19. (Personal communication, Jeffrey Davis, M.D., Wisconsin State Epidemiologist.)

Sporadic cases and several small outbreaks occurred in Illinois. Influenza A

FIG. 4 MAXIMUM EXTENT OF INFLUENZA-LIKE ACTIVITY, CUMULATIVE, DEC. 5, 1978 - MARCH 24, 1979



(H1N1)-like viruses were isolated from 20 specimens. (State of Illinois, Final Summary of Influenza Activity, 1978-79.)

4. West North Central. This area reported sporadic cases and focal and widespread outbreaks. Noteworthy was the isolation of influenza C in addition to influenza A and B. In Minnesota, an influenza A (H1N1) virus was recovered from a 21-year-old woman who had become ill on December 12. The first influenza A (H1N1) isolate in Missouri was obtained from an 11-year-old girl from the Kansas City area who had become ill on December 9. Outbreaks and influenza A (H1N1) isolates were reported from Nebraska by mid-January, and by early February, from Kansas and Iowa. Influenza A (H1N1) isolates were reported from North Dakota and South Dakota.

Influenza C viruses were isolated from two pediatric patients hospitalized at McConnell Air Force Base, Kansas (see Section E.3).

Between April 24 and May 1, 127 (36 percent) of 351 elderly residents in a Minnesota nursing home facility developed febrile respiratory illness (see Section E.6). Influenza B was isolated from 11 of 19 throat culture specimens, and 18 of those 19 persons showed fourfold antibody rises to influenza B.

5. South Atlantic. Focal and widespread outbreaks occurred in this area. In Florida, the first influenza A (H1N1) virus was isolated from a 34-year-old serviceman at Eglin Air Force Base in mid-December. Subsequently, outbreaks and the isolation of influenza A (H1N1) viruses were reported from Florida and Georgia. In early December, an outbreak of influenza-like illness occurred among students in a private school in Boca Raton, Florida. During the third week of December, influenza A (H1N1) viruses were isolated from children and young adults with febrile upper respiratory infections, who had visited an ER and pediatric practice in Hollywood, Florida. School absenteeism increased, and sporadic outbreaks were reported in South Georgia following Christmas. In early January, outbreaks of influenza-like illness among schoolchildren were reported in Cherokee County, North Carolina, and influenza A (H1N1) viruses were isolated from sporadic cases in South Carolina from persons aged 11, 14, and 15 years. Influenza A (H1N1) viruses were isolated from an outbreak among students at the University of Georgia in Athens during January. Eight influenza A (H1N1) viruses were isolated from military personnel in Maryland during an outbreak in late January. In early February, isolates were also reported by North Carolina and by Virginia.

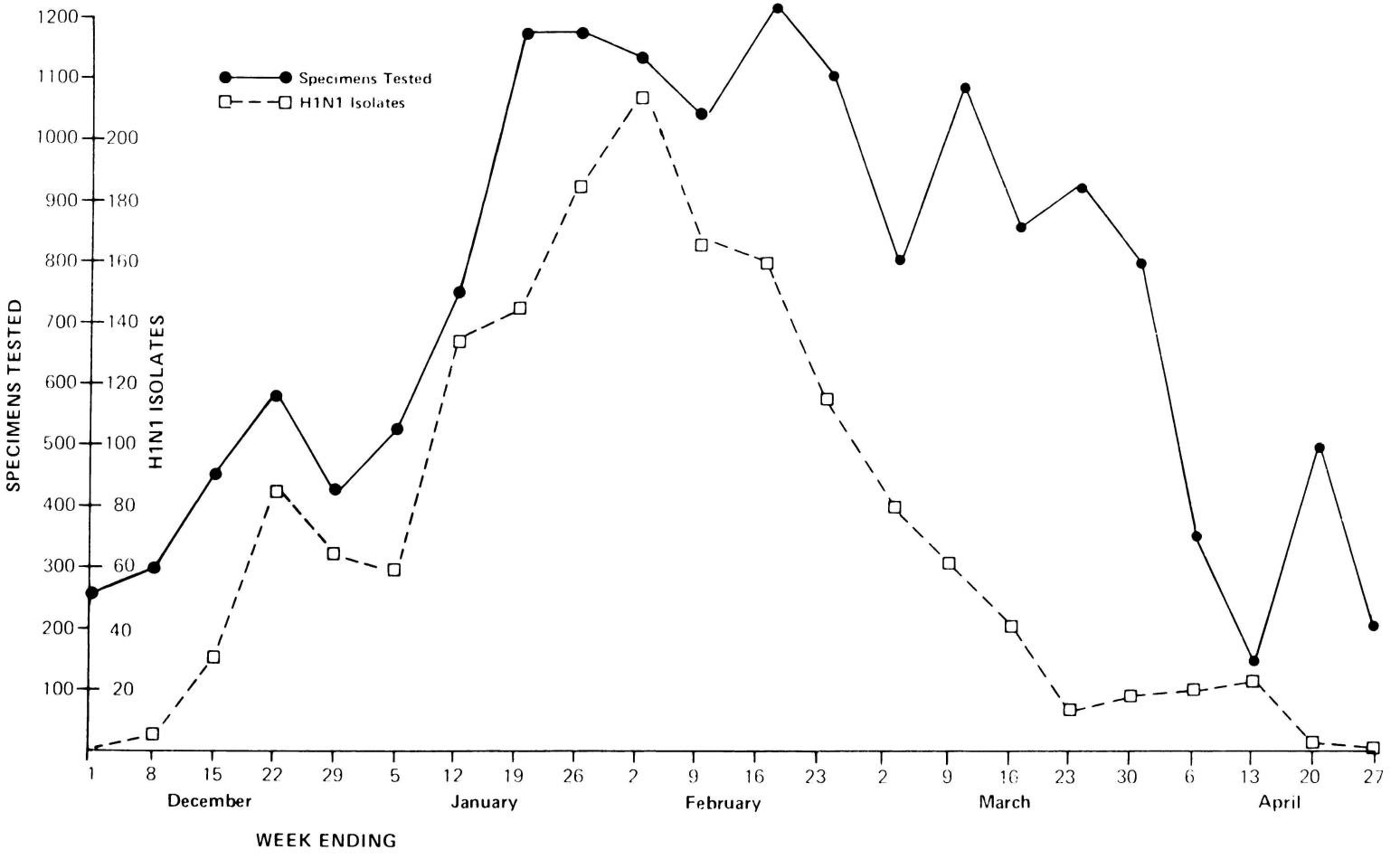
6. East South Central. The first reported outbreak in Mississippi involved a public school in Jackson in early January. Normal absenteeism in this school was 5-6 percent, but reached 40 percent on January 9. An influenza A (H1N1) virus was isolated from this outbreak. By mid-January, outbreaks and influenza A (H1N1) isolates had been reported from Alabama, activity had peaked in Mississippi, and influenza A (H1N1) viruses had been recovered from an outbreak among students at Vanderbilt University in Tennessee. Kentucky reported one isolate. In Starkville, Mississippi, a cluster of pneumonia cases occurred coincidentally with an influenza outbreak. Mycoplasma pneumoniae was isolated from several of these cases (Mississippi Weekly Morbidity Report, February 9, 1979; Mississippi Weekly Morbidity Report, January 12, 1979).

7. West South Central. Sporadic cases and outbreaks were reported from this area. The first influenza A and B isolates reported in the United States during 1978-1979 were in Texas. The earliest influenza B isolate involved a patient with respiratory illness seen at the U.S. Air Force Hospital, Bergstrom Air Force Base, Texas, on September 28. The first isolates of influenza A were reported by the Influenza Research Center, Baylor College of Medicine, Houston. Throat swabs obtained from four patients in Houston between October 18 and October yielded influenza A (H1N1) virus. Influenza A (H1N1)-like viruses were isolated from 11 new recruits at Lackland Air Force Base, Texas, on December 11. Additional influenza A (H1N1) viruses were isolated from sporadic cases in Houston in mid-December, at a time when increased school absenteeism was noted. By the end of January, however, the number of influenza-like cases reported in Texas was lower than that reported for the same time in 1978 (Texas Morbidity, Number 5, February 3, 1979).

The first influenza A (H1N1) virus in Louisiana was isolated from a 25-year-old pregnant woman who had become ill on December 20. By early February, outbreaks and influenza A (H1N1) isolates had been reported from Arkansas and isolates from Oklahoma.

8. Mountain. Focal and regional outbreaks of influenza-like illness occurred in

Fig. 5. Laboratory Surveillance for Influenza Virus Infections, 1978/79
Virus isolations by WHO collaborating laboratories (including military sources) in the U.S.



this area. Reported outbreaks among schoolchildren resulted in markedly increased absenteeism throughout Idaho beginning in early December. Influenza A (H1N1)-like viruses were isolated from eight persons under age 26 in Utah in mid-December, with school absenteeism as high as 50 percent in some areas of the State. In Arizona in mid-December, widespread outbreaks were reported at schools at the same time that influenza A (H1N1) viruses had been isolated from several counties. In late December, additional outbreaks and influenza A (H1N1) isolates were reported from Colorado, New Mexico, and Idaho. In Utah, increased school absenteeism recurred following the Christmas holidays. However, by the last week in January, school absenteeism and case reporting by physicians indicated a decline of influenza-like activity (Utah Communicable Diseases, January 1979). Malta and Great Falls, Montana, reported outbreaks during the first week in January. In the ensuing weeks, almost every community in the State experienced outbreaks characterized by increased school absenteeism. By mid-January, outbreaks had been reported from Wyoming, and influenza A (H1N1) viruses had been isolated in Idaho and Nevada. Influenza A (H1N1) virus was isolated in Wyoming by early February (Epidemiologic Notes and Comments, Montana Influenza Summary, 1978-1979).

9. Pacific. Sporadic cases and outbreaks occurred early during the influenza season and were followed by widespread outbreaks. In mid-October, an outbreak of influenza-like illness occurred among students in a parochial high school in Santa Barbara, California; instructors and staff were not affected. Paired sera subsequently demonstrated diagnostic antibody rises to influenza A (H1N1). An influenza H1N1-like virus was isolated from a 5-month-old boy in Los Angeles who had been ill in late October, when there was no evidence of local epidemic activity. During October to mid-November, several outbreaks of influenza-like illness among persons less than 25 years old were reported in Ventura and Santa Barbara counties. Influenza A (H1N1) viruses were isolated from siblings aged 9, 11, and 12 in Santa Barbara County who had become ill on November 24 and 25. By December 11, outbreaks had been reported in many areas of the State, with absenteeism reaching 50 percent in some schools. School absenteeism remained elevated in much of the State through mid-December, before schools closed for the holidays. Influenza C was isolated from a 22-year-old patient in Los Angeles, who developed an upper-respiratory infection on November 18.

An outbreak in the Los Angeles area provided an opportunity for detailed epidemiologic investigation (see Section E.1). An elementary school and a high school were chosen for study. Fifteen of 27 throat swabs obtained from ill students yielded influenza A (H1N1) viruses. There were no deaths attributable to influenza.

In mid-December, an outbreak of influenza-like illness occurred in a Centralia, Washington, junior high school (see Section E.2). Fourfold antibody rises to influenza A (H1N1) virus were indicated by hemagglutination inhibition testing in five persons.

By late December, in addition to California and Washington, outbreaks and isolates had been reported from Oregon, and sporadic cases and isolates from Hawaii. Following Christmas vacation, outbreaks among schoolchildren again occurred in Washington and Oregon through mid-January. By the end of the month, outbreaks and isolates had also been reported from Alaska.

Diagnostic antibody rises to influenza B were detected in sera obtained from four residents in a Seattle nursing home who had become ill between mid-March and May 1. The overall attack rate was 24 percent.

10. Territories. In mid-November, sporadic cases of influenza were reported among U.S. Coast Guard personnel in Puerto Rico. Influenza A (H1N1)-like viruses were isolated from some of these cases. An influenza A (H1N1) virus isolate was reported from the Virgin Islands.

C. Laboratory Reports

1. Virus Isolation Reports. Information was received from the same sources as in 1977-78 (see Section II.C). In contrast to previous years, few comments were received about difficulty of isolating influenza A (H1N1) viruses.

Reports received of virus isolations indicated that during the winter of 1978-79 in the United States, influenza A (H1N1) virus was first isolated in Houston, Texas, from a Mexican national who sought treatment for respiratory illness and who was cultured on October 22, 1978. Reported isolations peaked in January and February, and by April, only small numbers of isolates were being found (Figure 5). A total of 1,647 influenza A (H1N1) virus isolates were reported during the winter from State, county, city, and military laboratories that participate in the weekly reporting system coordinated by the WHO CCI. Of 1,103 isolates

TABLE 7
Influenza Isolates Received at WHO Collaborating Center for Influenza, CDC,
October 1978 - September 30, 1979

	A/Brazil/78	A/USSR/77	Other H1	B
NEW ENGLAND				
Maine	5			
New Hampshire	4			
Vermont	14	1		
Massachusetts	3			
Rhode Island				
Connecticut	12			
MIDDLE ATLANTIC				
New York	61			
New Jersey	20	1		
Pennsylvania	5		2	
EAST NORTH CENTRAL				
Ohio	3			1
Indiana				
Illinois	12	1		4
Michigan	23			
Wisconsin	8	1		4
WEST NORTH CENTRAL				
Minnesota	12			7
Iowa	1			
Missouri	13			
North Dakota	2			
South Dakota	5			
Nebraska	12			
Kansas	15			
SOUTH ATLANTIC				
Delaware				
Maryland	8			
District of Columbia				
Virginia	8			
West Virginia				
North Carolina	10			1
South Carolina	10			
Georgia	102		1	
Florida	30			

	A/Brazil/78	A/USSR/77	Other H1
EAST SOUTH CENTRAL			
Kentucky	1		
Tennessee	11		
Alabama	6		
Mississippi	46		
WEST SOUTH CENTRAL			
Arkansas	1		
Louisiana	14		1
Oklahoma	7		
Texas	70	1	3
MOUNTAIN			
Montana			
Idaho	3		
Wyoming	2		
Colorado	10		
New Mexico	26		
Arizona	19		1
Utah	34		
Nevada	11		
PACIFIC			
Washington	8		
Oregon	11		
California	44		1
Alaska	35		
Hawaii	15		
TERRITORIES			
Guam			
Puerto Rico	8		
Virgin Islands	1		
TOTAL	781	5	9

for which the age of the patient was given, only 65 (5.9 percent) were from persons 26 years of age or older, similar to 1977-78.

No influenza A (H3N2) isolates were confirmed in the United States during the winter, but a single A/Texas/1/77-like virus was recovered in July 1979 from a student in Washington, who had just returned from Taiwan.

One swine influenza virus was isolated from a college student in Texas, who became ill shortly after acting as a judge of swine exhibited at an agricultural show.

Influenza B activity was detected sporadically, with single isolates being recovered in San Antonio, Texas, in October 1978; in Los Angeles, California, in December; in Salt Lake City, Utah, in January; and in Ohio, in March. Several influenza B isolates were recovered in Wisconsin in February, March, and April, and in Illinois in March. Outbreaks caused by influenza B occurred in several nursing home populations, with one each occurring in California (late June), Minnesota (April-May), and Washington (April-May), as proved by serologic diagnosis and/or virus isolation. Influenza B was isolated in Hawaii throughout the summer, primarily from sporadic cases, but also from a small outbreak in a youth camp.

Influenza C viruses were also isolated during the winter--one in Los Angeles, California, in November 1978, from a young adult employee in the UCLA pediatric infectious disease unit, and two in Kansas in February 1979, from infants who were USAF dependents. A mixed isolate of influenza A (H1N1) and influenza C was recovered from one of the infants, but serologic studies on the case failed to support a mixed infection, although they did confirm that an outbreak of influenza C had occurred in 1- to 2-year-old children seen at the U.S. Air Force Base clinic.

2. Antigenic Analysis of Isolates Submitted

a. Influenza A (H1N1) Viruses. About 870 influenza A (H1N1) viruses were submitted (Table 7). Of these, all but 45 were characterized as similar to A/Brazil/11/78 when tested with ferret sera and with one or more monoclonal antibodies (Table 8). Only five isolates were similar to A/USSR/77; two isolates appeared similar to A/Peru/1/78 which in turn is similar to A/Lackland/7/78 (see Section III.C.2), and five isolates appeared similar to a new variant, A/Texas/23/79. These variants were most readily detected using monoclonal antibodies and showed very small differences from A/Brazil/11/78 when tested with ferret sera. However, an additional variant, A/California/45/78, exhibited a higher degree of drift away from A/Brazil/11/78. Only a small number of isolates were received from foreign sources. Both A/Brazil/78-like and A/USSR/77-like isolates were identified, with the former predominating. Among the variants received from abroad were two viruses from the USSR (reference A/USSR/50/79) that had a previously undetected reaction pattern as determined with monoclonal antibodies. Other variants from abroad included several viruses similar to either 1947 or 1953 reference strains of questionable geographic origins (including viruses from Fukushima, Japan), one virus from Peking similar to the variant A/Arizona/14/78 (see Section III.C.2), and several viruses from Japan similar to the A/Texas/23/79 variant.

b. Influenza A (H3N2) Isolates. The small number of influenza A (H3N2) viruses received early in 1979 were generally well inhibited by antisera to A/Texas/77. However, two viruses isolated in August in Thailand, A/Bangkok/1 and 2/79, showed significant drift from A/Texas/77 or other earlier influenza A (H3N2) isolates. One isolate from Taiwan in July (A/Taiwan/2/79) appeared quite similar to A/Bangkok/1/79, whereas another isolate from the same time (A/Taiwan/1/79) was broadly cross-reactive with A/Texas/1/77 and A/Bangkok/1/79 (Table 9). No significant drift in antigenic specificity of the remainder was detected.

c. Influenza B Viruses. Influenza B viruses were generally heterogenous, as in previous years. Many isolates were well inhibited by antisera to B/Hong Kong/5/72, but other isolates (e.g., B/Singapore/222/79) did not react so well with such sera. Antisera to newer isolates were generally more broadly reactive. One distinct variant was found (B/Singapore/263/79), and some other viruses appeared fairly similar to this variant (e.g., B/Buenos Aires/37/79) (Table 10).

d. Influenza C Viruses. Reciprocal hemagglutination-inhibition reactions of influenza C viruses indicated that isolates from recent years exhibited slight antigenic drift away from the reference viruses of 1947-50 (Table 11).

TABLE 8
Hemagglutination-Inhibition Reactions of Influenza A(H1N1) Viruses From USSR

	Ferret Sera							Monoclonal Antibodies†				
Reference Antigens	A/USSR/92/77*	A/Brazil/11/78	A/Arizona/14/78	A/Lackland/3/78	A/Peru/1/78	A/Texas A & M/23/79	A/California/45/78	W 18/1	70/1	110/1	264/7	385/1
A/USSR/90/77	640	1280	320	20	80	640	40	3,200	25,600	1,600	3,200	800
A/Brazil/11/78	160	1280	160	320	80	640	40	1,600	25,600	800	100	800
A/Arizona/14/78	80	320	1280	320	160	320	160	800	51,200	800	<100	800
A/Lackland/3/78	160	320	160	1280	80	320	160	<100	25,600	1,600	<100	1,600
A/Peru/1/78	80	320	640	320	1280	640	80	3,200	<400	1,600	<100	1,600
A/Texas A & M/23/79	40	640	160	320	80	640	80	100	51,200	800	<100	3,200
A/California/45/78	<20	80	40	80	20	80	320	<100	25,600	800	<100	<100
Test Antigens												
A/USSR/46/79	80	640	160	160	20	320	40	400	51,200	800	<100	800
A/USSR/50/79	160	160	80	80	<20	80	<20	800	12,800	400	100	<100
A/USSR/61/79	160	160	160	80	<20	80	<20	800	12,800	400	100	<100

*Serum to recombinant with Neq1
†Provided by Dr. R.G. Webster

Boxed values show reactions ≥eightfold lower than the homologous reaction with A/USSR/77

TABLE 9
Hemagglutination-Inhibition Reactions of Influenza A(H3N2) Isolates

	Ferret sera			
Antigens	A/Texas/1/77	A/Taiwan/1/79	A/Bangkok/1/79	A/Bangkok/2/79
A/Texas/1/77	2560	1280	640	320
A/Taiwan/1/79	1280	2560	640	1280
A/Bangkok/1/79	640	1280	2560	320
A/Bangkok/2/79	640	1280	160	5120

TABLE 10
Hemagglutination-Inhibition of Influenza B Isolates

	Ferret sera			
Antigens	B/Hong Kong/5/72	B/Singapore/222/79	B/Singapore/263/79	B/Buenos Aires/37/79
B/Hong/Kong/5/72	160*	320	<10	15
B/Singapore/222/79	40	480	60	40
B/Singapore/263/79	15	120	480	160
B/Buenos Aires/37/79	10	40	80	160

*All results are the mean of two tests

TABLE 11
Antigenic Drift in Recent Influenza C Isolates

	Hemagglutination inhibition with ferret sera	
Antigens	C/Ann Arbor/1/50	C/Kansas/1/79
C/Ann Arbor/1/50	640	160
C/California/1/78	160	160
C/Kansas/1/79	160	1280

3. Identification of Recombinant Viruses among Natural Isolates. After demonstrating in 1977-78 that mixed infections with influenza A (H1N1) and influenza A (H3N2) strains had occurred (see Section III C.3), a study was begun to detect recombinants among isolates received in 1978-79. Screening by Neuraminidase Inhibition (NI) tests of about 50 isolates with H1 hemagglutinin failed to detect any influenza A (H1N2) recombinants.

RNA hybridization techniques, however, revealed that influenza A (H1N1) viruses isolated in the United States during the winter of 1978-79 possessed four genes of influenza A (H3N2) origin, these being genes involved in RNA syntheses (i.e., RNAs 1, 2, 3, and nucleoprotein). These findings confirmed reports obtained by other workers using oligonucleotide mapping procedures.[8] Influenza A H3-containing viruses all appeared to have N2 neuraminidase and other genes of influenza A (H3N2) origin. Retrospective analysis of several influenza A (H1N1) viruses from 1977-78 which had the A/Brazil/78 hemagglutinin (present in epidemic viruses from 1978-79) found no evidence for these viruses containing any influenza A (H3N2) genes.[9]

4. Serologic Responses to Influenza A/USSR/77 Vaccine. Serum HI antibody responses to influenza A/USSR/77 were compared to responses to A/Brazil/11/78 among volunteers given influenza A/USSR/77 influenza vaccines during trials conducted in 1978 by the National Institute of Allergy and Infectious Diseases (NIAID), Food and Drug Administration (FDA), and CDC. Among individuals not previously infected with influenza A (H1N1) strains, the homologous antibody titers to A/USSR/77 vaccine were higher than were heterologous responses to the A/Brazil strains, which were first recognized in 1978 (Table 12). For example, the

TABLE 12

HI Antibody Titers in Sera from Selected Individuals* after Administration of Influenza A/USSR/77(H1N1) in Mid-1978 (NIAID, BoB, CDC Vaccine Study)

Age in Yrs. (Mid-'78)	No. Tested	Serum	Virus Strain†	Cumulative % with HI Titer ≥10	≥20	≥40	≥80	≥160	Cumulative No. (%) with ≥4-Fold Rise	GMT#
3-13	90§	Pre	A/USSR/77	--¶	--	--	--	--		5
			A/Brazil/78	--	--	--	--	--		5
		Week 6 (2 wks. after dose 2)	A/USSR/77	100	94	61	31	15	85 (94)	42
			A/Brazil/78	89	52	21	10	3	46 (52)	16
60	30@	Pre	A/USSR/77	37	3	--	--	--		7
			A/Brazil/78	47	27	3	--	--		8
		Week 4 (after dose 1)	A/USSR/77	100	100	90	70	47	29 (97)	105
			A/Brazil/78	100	97	83	73	53	27 (90)	105

*Sera tested from individuals with previously demonstrated ≥fourfold rise in HI antibody titer to A/USSR/77

†Influenza A (H1N1) viruses used in HI test after 5 and 7 egg passages, respectively

#Titers <10 assigned a value of 5 for calculation of GMT

§58 given Parke Davis, 32 given Wyeth. Dose 1: A/USSR/77 (2.3, 7 or 20 μg HA); dose 2: A/USSR/77, A/Texas/77, B/Hong Kong/72 (2.3/2.3/2.3, 7/7/7 or 20/20/20 μg HA)

¶-- indicates zero

@15 given Parke Davis, 15 given Connaught. Only dose 1 given: 7 μg HA

prevalence of HI antibody at titers ≥40 were 61 percent and 21 percent to A/USSR/77 and A/Brazil/78, respectively, after two doses of A/USSR vaccine (geometric mean titers of 42 and 16, respectively) in 90 individuals aged 3 to 13 years, while in 30 adults aged 16 or above, the prevalence of antibody titers at comparable levels were 90 percent and 83 percent to the homologous A/USSR/77 and heterologous A/Brazil/78, respectively (geometric mean titers of 105 for both). These results confirm the antigenic drift between A/Brazil and A/USSR previously demonstrated with ferret sera.

5. Heterotypic HI Antibody Responses to Influenza A (H1N1) Virus Associated with Influenza B Infections. During laboratory studies of an outbreak of influenza B virus, it was observed that HI tests demonstrated significant (fourfold or greater) rises in titer to influenza A (H1N1) virus in about one-third of individuals proven by virus isolation, HI, and complement fixation (CF) tests to have been infected with influenza B. No influenza A (H1N1) virus was circulating in the community at the time. This finding indicated the possibility that influenza B virus infections caused heterotypic antibody responses to influenza A (H1N1) virus in some individuals. No explanation for this observation has been found.

6. Vaccine Study, University of Georgia. From October 1978 to February 1979, a study of the immunogenicity, side effects, and protective efficacy of influenza A (H1N1) vaccine was conducted among 18- to 23-year-old college students. A second group of students received a hybrid influenza A (H1N2) vaccine to determine if individuals who were born after 1957, and thus unprimed to both the hemagglutinin (HA) and neuraminidase (NA) of the influenza A (H1N1) vaccine, would respond better to an influenza A (H1N2) vaccine having a familiar NA, to which these students would have been primed by prior infections with influenza A (H2N2) and influenza A (H3N2) viruses.

Only students with prevaccination serum HI antibody titers <10 to influenza A/USSR/77 ("sensitive" ether treated (ET) virus used in HI test) were enrolled. Each student received two doses (6-7 µgm HA in each dose) of WV or split influenza A vaccine either as influenza A (H1N1) virus (169 students) or influenza A (H1N2) virus (186 students) or of a placebo without virus (181 students). Influenza A (H1N1) vaccines contained A/USSR/77-like virus, and hybrid influenza A (H1N2) vaccines contained virus with A/USSR/77-like H1 HA and a 1965 "Asian" N2 NA. Quality control testing of the H1N1 and H1N2 vaccines indicated that the H1N2 vaccine although active had a lower HA concentration than did the H1N1 vaccine.

The percentage of students with A/USSR/77 HI antibody titers ≥40 at 4 weeks after the first dose was 53 percent for influenza A (H1N1) and 20 percent for (H1N2) recipients, respectively ($p<0.0001$); at 2 weeks after the second dose, the percentages were 74 percent and 34 percent, respectively ($p<0.0001$). Higher antibody titers followed vaccination with WV than with ET virus ($p=0.0007$). After the second vaccine dose, HI antibody to the A/Brazil/11/78-like (A/Georgia/79) epidemic strain of virus was present at titers ≥40 in 43 percent of influenza A (H1N1) and 18 percent of influenza A (H1N2) vaccine recipients.

In study weeks 11-14, an epidemic of A/Brazil/78 (H1N1)-like virus occurred. The attack rate of influenza-like illness was 40 percent among placebo recipients, while attack rates in influenza A (H1N1) vaccine recipients was 31 percent and in influenza A (H1N2) vaccine recipients was 29 percent. The differences from the placebo recipient rate were marginally significant. Forty-nine percent of placebo recipients exhibited fourfold titer rises to influenza A (H1N1) during the epidemic period, while 25 percent of influenza A (H1N1) vaccine recipients ($p<.0001$) and 40 percent of influenza A (H1N2) vaccine recipients ($p=.07$) showed fourfold increases. The attack rate for influenza-like illness among individuals who showed a fourfold titer rise was lower among influenza A (H1N1) recipients (14 percent) than among placebo recipients, whereas the attack rate among influenza A (H1N2) vaccine recipients (19 percent) was not significantly different from the placebo attack rate. In this group of serologically proven influenza illnesses, vaccine efficacy of 44 percent was shown for the influenza A (H1N1) vaccine.

Protection was correlated with the post-vaccination antibody titer to the A/Georgia/79 epidemic strain; among those with HI antibody titer ≤20 after influenza A (H1N1) vaccination, the incidence rate of illness with serological evidence of infection was 20 percent (19/97), compared with 6 percent (4/72) among those with post-vaccination titers ≥40. (Reported by Walter J. Brown, Jr., M.D., University of Georgia Health Service, Athens, Georgia; Bureau of Laboratories, Bureau of State Services, CDC.)

D. International Reports, 1978-79

The two subtypes of influenza A (H1N1) and influenza A (H3N2), as well as

TABLE 13

Isolations of Influenza Viruses Worldwide, by Month of First Report, October 1978--September 1979*

Month of First Report	Virus Type (Subtype)		
	A(H3N2)	A(H1N1)	B
October 1978		Australia Malaysia United States	Hong Kong New Zealand United States
November	Hungary Israel	France Jamaica Pakistan Singapore Spain Thailand United Kingdom	USSR
December	Bulgaria USSR	Algeria Austria Bulgaria Canada Canal Zone Egypt Germany Netherlands Philippines USSR	
January 1979	Canada Italy United Kingdom	Czechoslovakia Finland Greece Israel Italy Japan Romania Sweden Switzerland	Bulgaria Canada Germany Spain
February		Denmark Korea New Zealand	France Norway Sweden United Kingdom
March	Austria China France Hong Kong India	Australia† Hungary India	Brazil Denmark India Indonesia Netherlands Switzerland
April	Mongolia	Niue, South Pacific	Australia† Hong Kong Singapore
May	Jamaica Malaysia		Chile Malaysia Taiwan
June	Singapore USA (imported from Taiwan)	Argentina Madagascar Malaysia†	
July	Taiwan	Taiwan	Argentina Hawaii
August	Thailand Indonesia		
September		Brazil Germany Japan	

*From Weekly Epidemiological Record, 1978-1979, and other reports to the WHO Collaborating Center for Influenza, Atlanta and London

†Second appearance in this 12-month period

influenza type B, which were all prevalent in the preceding influenza season, continued to circulate in the 1978-79 winter (Table 13). Influenza A (H1N1) was reported from all areas of the world, generally causing only limited numbers of localized outbreaks or sporadic cases, although these did reach epidemic proportions in a few countries. Illnesses were again limited predominantly to those who had not had previous experience with these strains during their period of circulation between 1947 and 1957. An increasing proportion of the strains were antigenically close to A/Brazil/78 in many parts of the world, including Europe, Asia, and the Southern Hemisphere. Some of these influenza A (H1N1)viruses also contained four genes derived from influenza A (H3N2) strains.[8]

Influenza A (H3N2) was isolated in fewer countries than influenza A (H1N1), and the disease was usually sporadic. However, outbreaks of influenza associated with H3N2 infection occurred in Thailand and Hong Kong, and the virus was also reported in much of Asia and Europe, as well as Jamaica and Canada. Most of these influenza (H3N2) strains were most closely related to A/Texas/1/77 although A/Bangkok/1/79-like variants were detected. Influenza B virus activity was generally sporadic, although some outbreaks occurred in Australia, Bulgaria, Federal Republic of Germany, and North Europe, as well as in several countries of Asia, China, Chile, and Papua - New Guinea.[10]

E. Epidemic Investigations

1. Influenza - California. On December 11, 1978, a California school district reported that increases in absenteeism from baseline levels of less than 10 percent to approximately 23 percent were attributable to an influenza-like illness. Two schools, an elementary school and a nearby senior high school, were selected for viral and epidemiologic studies.

Eight of 14 throat swabs obtained from the elementary school students and 7 of 13 from the high school students yielded influenza A (H1N1) virus. A telephone survey was conducted of the households of 250 students selected at random from each school. Illness was considered influenza if it occurred from December 4-15, and caused fever and at least two of the following: headache, myalgia, cough, and sore throat.

Seventy-four of 184 (40.2 percent) of the elementary and 99 of 185 (53.5 percent) of the high school students experienced illnesses that fit this case definition. The peak date of onset occurred in the high school on December 10 and in the grade school on December 13. The median duration (4 days) and median number of days absent (3 days) were the same for both schools. The frequency of nausea and vomiting in the elementary school (41.7 percent and 28.4 percent, respectively) was higher than in the high school (31.3 percent and 17.2 percent, respectively). The prevalence of diarrhea was approximately the same in both groups (17.6 percent of the elementary and 18.1 percent of the high school students). More of the elementary students visited physicians than did high school students (29.7 percent vs. 18.1 percent). No deaths attributable to influenza were reported from either school. (Reported by: Glendale Unified School District; S. Fannin, M.D., Los Angeles County Department of Health; J. Chin, M.D., State Epidemiologist, California Department of Health Services; Immunization Division, Bureau of State Services, CDC.)

2. Washington. In mid-December 1978, the Epidemiology Section, Department of Social and Health Services, Washington State, was notified that the State's first outbreak of influenza-like illness was occurring in Centralia Junior High School, Centralia. Illness in the students involved acute onset of fever, headache, sore throat, rhinorrhea, myalgias, and malaise. Gastrointestinal distress and persistent cough were also reported.

Paired acute and convalescent serum specimens showed fourfold or greater HI antibody titer elevations to influenza A (H1N1) in five persons. Influenza virus was not isolated from 20 people (including 5 who had titer elevations) who had onset of illness within the 24 hours before the culture was taken.

A review of the school's attendance records showed that 10 percent of the 538 enrolled students were absent on December 5. This figure rapidly increased to 40 percent on December 15. Between December 4 and December 22, a total of 432 students experienced illness with an attack rate of 80 percent. School absenteeism in cases ranged from 1 to 12 days; mean absenteeism was 3.2 days. Four patients reported complications requiring hospitalization, three had secondary pneumonia, and one had severe dehydration. All recovered without sequelae.

Absenteeism for the entire school district (3,423 students) peaked on December 22, when 26 percent (882) were absent. School was dismissed for Christmas vacation on that day. When school reconvened on January 2, 1979, the junior high school reported only 9.6

percent absenteeism, and the school district reported 10.2 percent absenteeism. (Reported by: Cascade Family Medical Clinic, Centralia, Washington; D. Bower, R.N., Centralia School District, Centralia; R. Cole, M.D., M.P.H., Lewis County Health District; Washington State Laboratories; J.W. Taylor, M.D., M.P.H., State Epidemiological Record, February 2, 1979; WHO Collaborating Center for Influenza, Bureau of Laboratories; Field Services Division,Bureau of Epidemiology; Immunization Division, Bureau of State Services, CDC.)

3. Influenza C Isolates - McConnell Air Force Base, Kansas. Type C influenza infections were confirmed in two pediatric patients hospitalized at McConnell AFB, Kansas. A limited seroepidemiologic assessment conducted at McConnell AFB in an age- and sex-matched control and in a test pediatric population indicated little evidence to suggest concurrent type A influenza antibody activity. (Reported by: Epidemiology Division, School of Aerospace Medicine, Brooks Air Force Base, Texas.)

4. Outbreak of Influenza in Nursing Students - Pennsylvania. An outbreak of influenza-like illness among 156 nursing students in a Pennsylvania community occurred during February. Two of three throat washings obtained on February 14 from students with febrile, upper-respiratory tract infections were positive for influenza A (H1N1) virus. Specimens from five other persons in the community (ages ranging from 9 to 25) were positive for the same strain.

A questionnaire was administered to 136 nursing students who lived in a residence hall adjacent to the 323-bed hospital. Fifty-eight (43 percent) had experienced onset of an influenza-like illness (defined as fever and two of these symptoms: cough, chills, headache, rhinorrhea, sore throat, and myalgia) in the period December 18-March 12. Patients ranged in age from 18 to 23. Symptoms included fever (100 percent), chills (88 percent), cough (86 percent), sore throat (84 percent), rhinorrhea and myalgia (79 percent), headache(78 percent), nausea (57 percent), eye pain (31 percent), diarrhea (29 percent), and vomiting (16 percent). Temperatures were recorded by 54 students and ranged from 99-104° F (37.2-40.0° C); the mean was 101.6° F (38.6° C). The mean number of days of confinement to bed was 3, and illness accounted for 120 days (2 days per person) of missed class time or hospital work. Forty-eight students made a total of 85 visits to physicians, clinics, or ER's. Vaccination histories were not obtained, but immunization had not been offered by the nursing school that year.

One case of presumed nosocomially acquired influenza was confirmed in a patient at the hospital. The patient, a 25-year-old woman, experienced an abrupt rise in temperature on February 23, 21 days following admission for a diagnostic evaluation. Throat swabs taken from her grew influenza A (H1N1) virus. (Reported by: E.S. Balkovic, M.S., F.B. Rose, M.D., Robert Packer Hospital/Guthrie Clinic, Sayre, Pennsylvania; B. Kleger, Dr.Ph., Pennsylvania Department of Health; Immunization Division, Bureau of State Services, CDC.)

5. Ft. McClelland, Alabama. From January 11-22, 1978, an outbreak of ARD occurred among military recruits at Fort McClelland, Alabama. The outbreak was investigated to determine the cause and to evaluate influenza vaccine efficacy. Hospital records, recruit health records, serology, and viral cultures were reviewed. Of 4,633 recruits, 1,110 were ill with ARD, and 152 required hospitalization.

One hundred and forty-five were hospitalized with an illness compatible with influenza. There were 102 males and 43 females; ages ranged from 16 to 22 years, with a mean of 20 years. Seven of 19 viral cultures yielded viruses: two were influenza A (H1N1), one was adenovirus, and four were parainfluenza III. Paired sera were collected from 81 recruits: 55 showed a fourfold antibody rise to influenza, but were negative for rises to other viruses. Immunization histories were known for 40 of the 55: 13 were vaccinated and 27 unvaccinated. Only 67 percent of the total recruit population had received one dose of either trivalent influenza vaccine (containing 20 µg each of A/USSR/77, A/Texas/77, and B/Hong Kong/72) or monovalent vaccine (60 µg A/USSR/77), and recruit companies with high immunization rates had the lowest attack rates. Vaccine efficacy based on confirmed serologic cases was 86 percent, whereas by clinical history it was 49 percent, indicating the diluting effect of other viruses causing similar illness. The results of this investigation suggest that vaccine which included at least 20 µg of A/USSR/77 antigen conferred protection against illness caused by strains circulating in 1978 similar to influenza A/Brazil/78. (Reported by Thomas Chester, M.D., Acting State Epidemiologist, Alabama Department of Public Health; Field Services Division, Bureau of Epidemiology; Immunization Division, Bureau of State Services, CDC.)

6. St. Paul Island, Alaska. During December 1978 and January 1979, an outbreak of influenza A (H1N1) occurred on St. Paul Island, Alaska. The strain causing this outbreak was documented by virus isolation to be A/Brazil/11/78-like. The illness was typical of recent influenza A(H1N1) with a high attack rate in individuals <25 years of age (71.6 percent) and a much lower attack rate in individuals ≥25 years of age (14.5 percent). The illness was mild and no serious complications occurred. Analysis of patients' sera for HI antibodies revealed similar rates of seroconversion against three H1N1 antigens: A/USSR/92/77, A/California/10/78, and A/Brazil/11/78. (Reported by Communicable Disease Section, Alaska Department of Health and Social Services; Field Services Division, Bureau of Epidemiology, CDC.)

7. Influenza B in a Minnesota Nursing Home. An outbreak of febrile respiratory illness occurred in a Minnesota nursing home between April 24 and May 21, 1979, and involved 129 (35.9 percent) of 359 residents. Throat swabs were obtained from 19 acutely ill residents: 11 yielded influenza B virus. Fourfold or greater rises to influenza B in CF or HI antibodies were detected in paired sera from 18 of the 19.

Three hundred thirty-three (93 percent) of the 359 residents had received trivalent influenza vaccine during November 1978. The attack rate in residents under 80 years of age was lower than that in residents over 80 years of age (24 percent versus 41 percent). The attack rate among those living in locked wards was 53 percent, compared to 33 percent among those in open wards ($p < .01$). The incidence rate of illness was not related to duration of residence at the nursing home, care status, or the number of roommates. However, the spread of infection did appear to be related to the place in which meals were taken.

Six of the 18 residents with diagnostic antibody titer rises to influenza B also had fourfold or greater rises to influenza A (H1N1) by HI testing, but no rises in CF antibody to influenza A occurred in any of the residents tested. There was no evidence of influenza A activity in the surrounding community or elsewhere in the State.

Forty employees who had received trivalent influenza vaccine in the preceding November were matched with 120 unvaccinated employees of the nursing home for job title and age. The vaccinated and unvaccinated groups were similar in mean age, sex, their degree of contact with the residents, shift and hours worked, and type of work.

A case was defined as fever plus sore throat, cough, or rhinorrhea, with onset during the epidemic period. Post-epidemic serum specimens were obtained from 25 employees fitting the case definition and from 85 who did not fit the case definition. The geometric mean complement-fixing antibody titer to influenza B was 21.1 in those who were ill versus 7.3 in those who were not ill.

The incidence rate of influenza-like illness was not significantly different in the vaccinated and unvaccinated groups: 11 (28.9 percent) of 38 in the vaccinated group vs. 22 (19.1 percent) of 115 in the unvaccinated group ($\chi^2=1.10$ NS). Thus, a significant protective effect of vaccination in this population could not be documented. (Reported by Andrew G. Dean, M.D., Minnesota State Epidemiologist; Field Services Division, Bureau of Epidemiology; Immunization Division, Bureau of State Services, CDC.)

V. TRIALS OF AMANTADINE AND RIMANTADINE CHEMOPROPHYLAXIS AND CHEMOTHERAPY, 1978

With the appearance of influenza A (H1N1) in late 1977, NIAID, in collaboration with CDC, the Department of Defense, and the Bureau of Biologics (BoB), FDA, conducted clinical trials with amantadine, a drug licensed for the prophylaxis and treatment of influenza, and rimantadine, an unlicensed analog of amantadine which some workers have reported to be as effective as and to produce fewer side effects than amantadine. Studies were conducted between January and April 1978, involving approximately 1,800 subjects. A summary of these studies has been reported.[11] In addition, a conference on amantidine was held at the National Institutes of Health on October 15-16, 1979, and a consensus on the drug's use developed (Appendix I).

In brief, the conclusions reached at the conference were: (1) Under appropriate epidemiologic and clinical conditions, amantadine hydrochloride should be used in the prevention and treatment of influenza caused specifically by strains of influenza A. For example, trials with amantadine demonstrated approximately 60 percent to 70 percent effectiveness in preventing illness caused by influenza A/USSR/77-like viruses; (2) amantadine hydrochloride should be considered complementary to active immunization with influenza vaccine in influenza control programs. Commercially available inactivated influenza vaccines should be given according to the annual recommendations of the Immunization Practices Advisory

FIG. 6. REPORTED CASES OF REYE SYNDROME AND PERCENTAGE OF INFLUENZA A VIRUS ISOLATES FROM RESPIRATORY SPECIMENS, BY WEEK OF ISOLATION, UNITED STATES, DECEMBER 3, 1977 – NOVEMBER 18, 1978

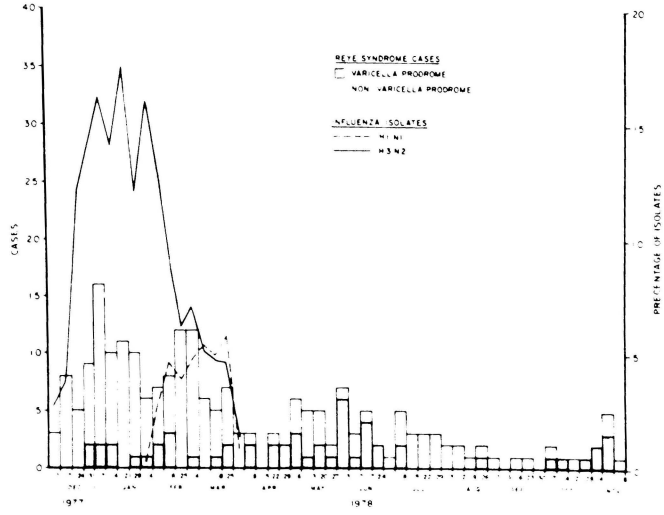


FIG. 7. REPORTED CASES OF REYE SYNDROME BY WEEK OF ONSET OF PRODROME AND INFLUENZA ISOLATES BY WEEK OF REPORT, UNITED STATES, DECEMBER 2, 1978 – NOVEMBER 30, 1979

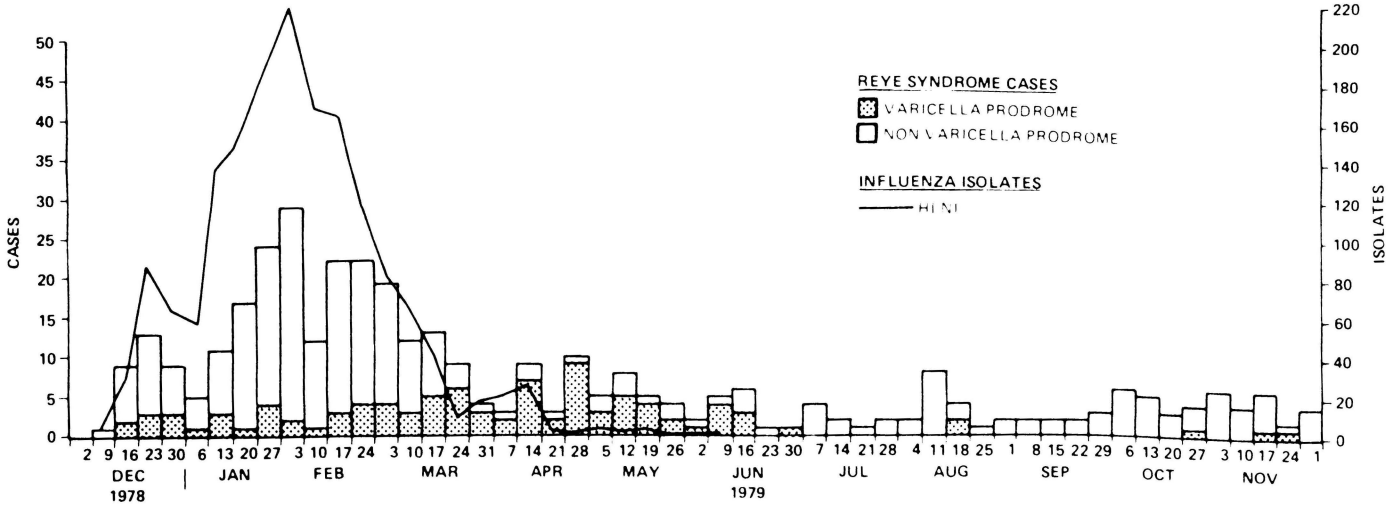
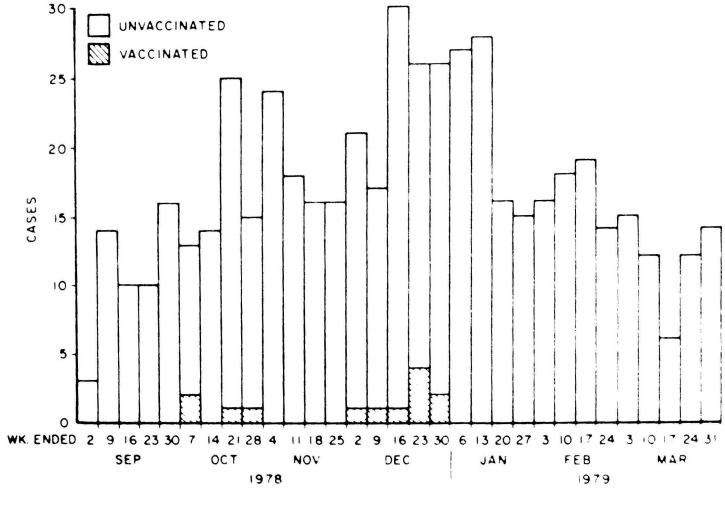


Fig. 8 CASES OF GUILLAIN-BARRÉ SYNDROME, BY WEEK OF ONSET OF NEUROLOGIC SYMPTOMS, UNITED STATES, SEPTEMBER 1, 1978 - MARCH 31, 1979



Committee (ACIP). However, amantadine should be considered for high-risk individuals who have failed to receive vaccine or when vaccines are not available for use before the occurrence of an influenza A epidemic.

VI. REYE SYNDROME

A. 1977-1978 Season

During the 1977-1978 season, 237 cases of Reye syndrome were reported to CDC (Figure 6). The majority of cases occurred between December and March, when epidemic respiratory diseases are usually seen in children. Using data collected through WHO Collaborating Laboratories as a measure of influenza-like activity, a temporal association was seen between the occurrence of Reye syndrome and the reporting of both influenza A (H3N2) and (H1N1) viruses. However, this association was not totally clear; Reye syndrome cases dropped in frequency before a decrease in isolations of influenza A occurred and clusters of Reye syndrome cases were not recorded in association with local outbreaks of influenza A. This is in contrast to the patterns in 1973-1974 and 1976-1977, when the epidemic curve for Reye syndrome cases more closely paralleled reported isolations of influenza B nationally, and outbreaks which were temporally and geographically associated with influenza B were reported in several States.

B. 1978-1979 Season

During the 1978-1979 season, 389 cases of Reye syndrome were reported to CDC (Figure 7). Using data collected through the WHO Collaborating Laboratories as a measure of influenza-like activity, a temporal association was observed between the occurrence of Reye syndrome and the reporting of influenza A (H1N1) virus isolates which peaked in late February and early March of 1979. Clusters of Reye syndrome cases were reported in eight States: Utah, Arizona, Colorado, Minnesota, Michigan, Ohio, Oklahoma, and Georgia. Nationally, the pattern of these outbreaks followed the occurrence of outbreaks of influenza A in each region, with the first cases of Reye syndrome occurring in the western United States, followed by cases on the Northeast and Midwest. Concurrent widespread influenza A activity was reported in all of these States. While influenza B has been epidemiologically associated with outbreaks of Reye syndrome in the 1973-1974 and 1976-1977 seasons, this was the first time that influenza A outbreaks had been associated with outbreaks of Reye syndrome in the United States.

VII. GUILLAIN-BARRÉ SYNDROME

A. 1977-1978 Season

A surveillance system for Guillain-Barré Syndrome was not established until 1978.

B. 1978-1979 Season

A CDC-American Academy of Neurology (AAN) sentinel-neurologist system was established in 1978 to detect cases of Guillain-Barré Syndrome (GBS). Approximately 37 percent of the AAN membership participated in the system.[12]

Surveillance was intensified between September 1978 and March 1979. A total of 544 cases of GBS with onset during this period were reported. Thirteen individuals with GBS, 12 of whom were 18 years or older, had been vaccinated within 8 weeks before onset of the disease and 393 had not (Figure 8). The relative risk of vaccine-associated GBS in this surveillance was 1.4 (95 percent confidence limits, 0.7 to 2.7). Among the 10 vaccinated patients with a known interval between vaccination and onset of GBS, the length of interval was randomly distributed throughout the 8-week period. No statistically significant excess risk of GBS was found after influenza vaccination in the 1978-1979 influenza season.

Beginning in late 1978, a registry of events following immunizations was established. Reported events following influenza vaccination for the 1978-1979 influenza season were minimal in number.

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Amantadine: Does It Have A Role in the Prevention and Treatment of Influenza?

A National Institutes of Health Consensus Development Conference on "Amantadine: Does it have a Role in the Prevention and Treatment of Influenza?" was held at NIH on October 15 and 16, 1979.

At NIH, consensus development conferences bring togehther biomedical research scientists, practicing physicians, consumers, and others as appropriate in an effort to reach general agreement on the safety and effectiveness of a medical technology. That technology may be drug, device, or medical or surgical procedure.

Amantadine hydrochloride (Symmetrel*) is an antiviral compound which is currently approved in the United States for the prevention and symptomatic management of the respiratory tract illness caused by influenza A virus strains. The antiviral activity of amantadine was reported 15 years ago and its efficacy in the prophylaxis of type A influenza was shown in clinical trials over 10 years ago.

Amantadine was approved in 1966 for use in the prevention of Asian (H2N2) influenza. However, this use of the drug has not received wide acceptance in the United States. The reluctance to use amantadine was due to several factors, including the inconvenience associated with the use of prophylactic drugs, concern about side effects, and most important, the fact that it was originally approved for use only with Asian (H2N2) influenza. Shortly thereafter, A/Hong Kong/68 (H3N2) strains appeared and caused pandemic influenza. Because of restrictions placed in the initial approval, amantadine could not be recommended for use against Hong Kong influenza until further clinical trials had been completed, by which time the pandemic had passed.

The major use of amantadine over the past years has been in the treatment of Parkinson's disease. This has provided experience with long-term use and side effects. By 1976, with the potential threat of swine influenza, sufficient data had been developed to justify changing the FDA approval to include prophylactic and therapeutic use of amantadine against all strains of influenza A virus.

This Consensus Development Conference was called to review the information available on the use of amantadine hydrochloride in the prevention and treatment of disease caused by influenza A. A panel was convened, consisting of individuals with various backgrounds but little or no personal involvement in research on amantadine hydrochloride. A group of experts with extensive knowledge and experience in the epidemiology of influenza, the evaluation of influenza vaccines, and the properties of amantadine hydrochloride presented and discussed the pros and cons of the several clinical uses of amantadine before the panel. The experts included scientists from the United Kingdom and Soviet Union, where there has been extensive experience with amantadine hydrochloride and its congener, rimantadine. The panel then met to consider five specific questions:

I. What are the potential benefits of the prophylactic and therapeutic uses of amantadine hydrochoride for influenza A infections?

II. Who should take amantadine hydrochloride and when should it be taken?

III. What are the risks associated with the use of amantadine hydrochloride?

IV. Is there a role for the use of amantadine hydrochloride in combination with vaccines?

V. Why has the medical profession not accepted amantadine hydrochloride in the prevention and treatment of influenza?

The following represents the consensus of the seven panel members. It must be recognized that there are specific aspects in the report with which individual members may have some reservations or even frank disagreements, but the disagreements were not of a magnitude to warrant inclusion of a minority report.

*Symmetrel is a du Pont registered U.S. trademark.

I. What are potential benefits of use of amantadine hydrochloride in the treatment of influenza type A?

Numerous studies have shown amantadine hydrochloride to have an efficacy of approximately 70 percent in the prevention of influenza caused by type A strains. Consideration of potential benefits must take cognizance of this.

The use of amantadine hydrochloride as a prophylactic measure and in the treatment of influenza A has significant potential value in reducing the morbidity associated with this disease and its complications. It is anticipated that this will be of particular value among those with cardiopulmonary disease, especially the elderly who have more severe and life-threatening forms of disease and are more likely to have pneumonic complications. This applies especially to the million and a half aged persons in long-term care institutions. Under epidemic conditions, the prophylactic and therapeutic use of amantadine hydrochloride among those who care for them could help maintain essential services in such institutions.

Similar beneficial effects are anticipated from use of the drug in vulnerable patients and those caring for them exposed to influenza A in hospitals. Other high-risk groups among whom beneficial results may be anticipated under epidemic conditions are essential public servants, such as policemen, firemen, and military personnel, especially those who have not had influenza virus vaccine immunization.

A reduction in the mortality from influenza A and its complications is a desirable goal which will have to be verified by close observation of those undergoing treatment with amantadine hydrochloride.

II. Who should take amantadine and when should it be taken?

The panel reviewed the manufacturer's approved recommendations, those suggested by experts, and the accumulated data. The panel agreed that amantadine has a role in both the prevention and treatment of influenza A. Amantadine is not effective against influenza B strains or against other respiratory viruses.

It was felt that the indications could be ranked by priority. Those indications with lower priority require a greater understanding between the physician and patient of the potential benefits, risks, and costs.

Prophylaxis

When amantadine hydrochloride is to be recommended, there must be both epidemiologic and virologic evidence of an outbreak of influenza A infection in the community or region. It should be recognized that influenza A outbreaks in communities extend over intervals of 4 to 6 weeks, not over periods of many months and that outbreaks caused by other viral agents (e.g., parainfluenza virus) may precede or follow influenza and be confused with influenza in their clinical presentations. Groups with highest priorities for receipt of amantadine hydrochloride include:

1. Unvaccinated children and adults at high risk of serious morbidity and mortality by virtue of underlying diseases, which include pulmonary, cardiovascular, metabolic, neuromuscular or immuno-deficiency diseases. Note should be made that dosage regimens have not been well defined in patients with renal insufficiency; hence, its use in this group of patients should be cautious.

2. Adults who have not been vaccinated with an appropriate contemporary influenza vaccine and whose activities are essential to community function, e.g., policemen, firemen, selected hospital personnel. Such persons are in frequent contact with individuals who may have influenza and should be considered at higher risk of contracting influenza than the general population.

3. Individuals in semi-closed institutional environments, especially older persons, who have not received the current influenza vaccine.

The groups for which the panel felt the benefit-risk considerations were less clear include all elderly patients (65 years or older) who have not received vaccine and household contacts of an index case.

The use of amantadine hydrochloride for prophylaxis in hospital patients in the presence

of a demonstrated outbreak should take into consideration local and particular risk factors and conditions; for example, the patient who is to undergo inhalation anesthesia may be at higher risk of serious complications.

The possible teratogenic risk of amantadine hydrochloride following administration to pregnant individuals is not fully known. The drug should be administered to pregnant women only after weighing the possible risks to the fetus against the benefits to the patient.

Therapy

To be therapeutically effective, amantadine hydrochloride must be administered as soon as possible and not later than 48 hours after onset of symptoms. Groups for which the panel felt therapy with amantadine hydrochloride should be strongly considered include:

1. High-risk patients as defined above.

2. Patients in whom the physician makes the diagnosis of life-threatening primary influenza pneumonia or infants with life-threatening influenza-associated croup.

3. Individuals whose positions are essential to community activities and for whom shortening of a symptomatic illness by 24 hours is judged important. It should be recognized that influenza is a mild disease in almost all otherwise healthy individuals, and that treatment with amantadine hydrochloride will not be necessary in most of these individuals. Initial evidence suggests that abnormalities in pulmonary function return to normal more rapidly in amantadine-treated patients than in non-treated patients.

III. What are the risks of the use of amantadine hydrochloride in the above-described fashions for the prophylaxis and treatment of disease caused by infleunza A viruses?

The risks and problems that may develop from the use of amantadine hydrochloride pertain to both the individual recipient of the drug and to broader public health concerns:

1. Direct side effects of the drug in individual patients: Numerous clinical trials involving over 11,000 subjects have been performed on amantadine prophylaxis for influenza A virus infections with careful evaluation of the side effects of the drug. Nervous system symptoms (insomnia, lightheadedness, nervousness, difficulty in concentration, or drowsiness) have been observed in up to 7 percent of individuals receiving amantadine (200 mg daily) in excess over control subjects receiving placebo. These effects tend to begin within several hours of receipt of a dose and are transient. If adverse symptoms do not develop in the first 48 hours after initiating prophylaxis or therapy, they are not likely to occur.

If symptoms develop, they often subside during continuing drug administration. Mild impairment of intellectual acuteness and decreased motor function may occur and may influence a physician's decision about whether to use such prophylaxis in the individual working at a very sensitive job requiring constant alertness. Other side effects occur at a lower frequency and are of a less serious nature.

Chronic use of amantadine hydrochloride (for over 5 or 6 months), as in the treatment of Parkinson's disease, may be associated with the development of livedo reticularis and peripheral edema; both resolve on omission of the drug. These findings do not appear to be a problem with the shorter course of the drug that would be employed in the prophylaxis or treatment of influenza A infections. The use of amantadine hydrochloride in elderly subjects, based on extensive experience with patients with Parkinson's disease, does not appear to present other special problems or side effects. However, such patients merit further study for possible adverse reactions since they represent a group of patients with a higher likelihood of various coexisting organ dysfunctions which may contribute to drug toxicity.

2. The potential for drug abuse: Thus far, there have been no reports of abuse of amantadine hydrochloride by individuals attempting to alter their state of consciousness. Amantadine hydrochloride does not appear to provide prominent analgesia or euphoria, effects that might suggest the potential for misuse. Although available information would suggest that abuse of this drug is rather unlikely, some caution is still merited in view of the limited use of the drug until now.

3. Selection of amantadine-resistant strains of influenza A as a result of extensive

prophylactic and therapeutic use of this drug: The spontaneous development of amantadine resistance among influenza A viruses in culture occurs at a relatively high frequency (about 1×10^{-4}). Although amantadine-resistant variants have not as yet been isolated as the predominant virus from patients who have received the drug, the possible selection of such strains in the population under the pressure of extensive amantadine therapy must be considered. Inappropriate use of amantadine hydrochloride for prophylaxis and treatment of viral respiratory infections due to viruses other than influenza A or the widespread use of the drug beyond the special groups of patients indicated earlier may encourage the development of such resistance while not providing protection from influenza A for the most vulnerable patients. If such were to transpire, the current salutory prophylactic effect of the drug might be lost for the patients who truly need it, those patients at highest risk for fatal complications.

IV. Role for combined use of amantadine hydrochloride and influenza immunization.

Immunization remains the primary method for prophylaxis against influenza. When amantadine hydrochloride is given for prophylaxis, it should be used as adjunctive therapy until the patient has received influenza vaccine and an immune response can be anticipated. Amantadine hydrochloride does not suppress the antibody response to inactivated influenza vaccine. If the patient has previously received vaccine containing antigen related to that of the current epidemic strain, an adequate antibody response can be anticipated in 70 to 80 percent of vaccinees approximately 10 days after vaccine administration. Administration of amantadine hydrocholoride can be discontinued at that time. Since vaccine efficacy is usually 70 to 80 percent, more prolonged administration of amantadine hydrochloride may provide an additional margin of protection for the elderly high-risk patient. If the patient has not received an antigenically similar vaccine in the past, administration of amantadine hydrochloride is continued for 4 to 6 weeks, assuming that influenza continues to occur in the community.

An immunocompromised individual may not respond adequately to influenza vaccine. When the antibody status of such a patient is uncertain, amantadine prophylaxis may be indicated.

V. Conclusions

1. Under appropriate epidemiologic and clinical conditions, amantadine hydrochloride should be used in the prevention and treatment of influenza caused specifically by strains of influenza A.

2. Amantadine hydrochloride should be considered complementary to active immunization with influenza vaccine in influenza control programs.

3. The public and the medical profession should be made more aware of the need for and approaches to preventing influenza.

VI. Unanswered Questions

During the discussion, the group recognized a number of areas in which the availability of further information would have rendered decisions easier. Such considerations, not necessarily listed in order of priority, include the following:

--Procedures and facilities to enable rapid diagnosis of influenza A virus infection

--Additional studies of efficacy in elderly patients

--Additional studies in infants and children

--Better understanding of the pharmacology and pharmacokinetics of amantadine hydrochloride in all age groups, especially children and and the elderly and in individuals with renal impairment

--The effect of amantadine hydrochloride on mortality due to influenza, especially primary influenza pneumonia

--Rimantadine as a congener which may be more effective and/or less toxic than amantadine hydrochloride

--Safety of amantadine hydrochloride in pregnancy

--Optimal regimens of dosage and duration of treatment

--Monitoring for the appearance of amantadine-resistant strains of influenza A virus.

The chairman of the conference was Jay P. Sanford, M.D., Dean, School of Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Members of the Consensus Development Panel were Mrs. Laryl Lee Delker, Panel on Bacterial Vaccines with Standards of Potency, Moorestown, New Jersey; Robert H. Moser, M.D., American College of Physicians, Philadelphia, Pennsylvania; John D. Nelson, M.D., University of Texas, Southwestern Medical School, Dallas Texas; Manuel Rodstein, M.D., The Jewish Home and Hospital for the Aged, New York, New York; Karl Rolls, M.D., Doctors Hospital Medical Complex, Sarasota, Florida; and Morton N. Swartz, M.D., Harvard Medical School, Cambridge, Massachusetts.

The views expressed in this summary statment do not necessarily reflect those of the NIH and the DHHS.

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Recommendations of the Public Health Service

Advisory Committee on Immunization Practices

Influenza Vaccine

INTRODUCTION

Influenza occurs in the United States every year, but with great variation in incidence and geographic distribution. It periodically becomes epidemic when the antigens of prevalent influenza viruses have changed enough for a significant proportion of the population to become susceptible. More epidemics are caused by influenza A viruses than by influenza B viruses, and influenza A epidemics are notable for causing mortality in excess of what is normally expected. Furthermore, only influenza A viruses undergo major antigen changes that result in pandemics (worldwide epidemics).

An example of the sudden appearances of antigenically distinctive influenza A viruses occurred in February 1976, when A/New Jersey/76 (swine) influenza virus was identified as the cause of a focal epidemic at Fort Dix, New Jersey. Recognition of the potential of this new virus for supplanting prevalent strains of influenza A, the threat of subsequent pandemic spread, and the Federal program to provide specific swine influenza vaccines in 1976 are well known. The fact that A/New Jersey/76 virus did not spread beyond Fort Dix makes it unlikely that this virus constitutes a risk in 1977-78. Nevertheless, because swine influenza viruses continue to exist in swine in the United States and to cause occasional human cases, primarily in those with agricultural exposures, the swine influenza vaccines remaining from 1976 have been stockpiled in the event of future need.

Thousands of persons have died of influenza in epidemics in the United States in the past 20 years. In the 1957-58 influenza season, when a new influenza A virus (Asian strain) appeared, nearly 70,000 deaths were attributed to it in this country alone. In 1968-69, when the Hong Kong variant caused widespread epidemics in the United States, there were an estimated 33,000 excess deaths. In the intervening years, whenever influenza A epidemics have involved most of the country, 10,000 to 20,000 excess deaths resulted.

Efforts to prevent or control influenza in the United States usually have been aimed at protecting those at the greatest risk of becoming seriously ill or dying. Repeated observations during influenza epidemics have indicated that deaths occur primarily among chronically ill adults and children and in older persons, especially those over age 65. These "high-risk" persons should be vaccinated annually regardless of the amount of influenza in their geographic areas.

In interpandemic periods, vaccinating the entire population has not been considered to be a reasonable public health objective for several reasons: the limited duration of protection from influenza vaccines, the relatively low attack rates of influenza in community outbreaks, and the usual lack of serious complications of disease in healthy people.

INFLUENZA VIRUS VACCINE FOR 1977-78

The Bureau of Biologics, Food and Drug Administration, reviews influenza vaccine formulation regularly and recommends reformulation with contemporary antigens when indicated. Bivalent influenza vaccine for 1977-78 will contain inactivated influenza A and B viruses representative of currently prevalent strains. Each adult dose of vaccine will contain 400 chick cell agglutinating (CCA) units of antigen or its equivalent in the following proportion: 200 CCA units of influenza A virus comparable to the prototype A/Victoria/3/75 (H3N2) and 200 CCA units of B/Hong Kong/5/72 influenza virus.

The 1977-78 vaccine will be available in "split-virus" and "whole-virus" preparations. Split-virus vaccines, which contain antigens produced by chemically disrupting the influenza virus, have been associated with somewhat fewer side effects than whole-virus vaccines, particularly in children. However, the split-virus vaccines appear to be somewhat less effective in eliciting antibodies when given as a single dose to persons who have not been "primed" by exposure to related viruses in nature or through vaccination.

The characteristic side effects and immunogenicity of split-virus and whole-virus influenza vaccines are important in understanding dosage recommendations for various age groups. Adults and older children, most of whom have had experience with influenza antigens related to A/Victoria/3/75 or B/Hong Kong/5/72 either by infection or through vaccination, can be expected to have a good antibody response to a single dose of the 1977-78 bivalent influenza vaccine. Children less than 6 years of age, some of whom have not encountered the currently prevalent viruses, will need 2 doses of vaccine given 4 or more weeks apart in order to achieve satisfactory antibody responses. These children will not be adequately protected unless the second dose is given. Furthermore, because children and adolescents tend to experience somewhat more side effects from influenza vaccine than adults, *only* split-virus vaccines should be given to persons less than 18 years of age.

VACCINE USAGE

General Recommendations

Annual vaccination is strongly recommended for adults and children of all ages who have such chronic conditions as: 1) heart disease of any etiology, particularly with mitral stenosis or cardiac insufficiency, 2) chronic bronchopulmonary diseases, such as chronic bronchitis, bronchiectasis, tuberculosis, emphysema, and cystic fibrosis, 3) chronic

renal disease, and 4) diabetes mellitus and other chronic metabolic disorders.

Vaccination is also recommended for older persons, particularly those over age 65 years, because excess mortality in influenza outbreaks occurs in this age group.

Vaccination may also be considered for persons who provide essential community services and may be at increased risk of exposure. Vaccination of such persons and of patients not specified in the high-risk groups should be made on an individual basis giving consideration to the inherent benefits, risks, and costs.

The accompanying table (see p. 199) summarizes vaccine and dosage recommendations by age group for 1977-78. These recommendations are derived from observations made during the field trials of influenza vaccines conducted in 1976. Because information from the immunization of infants and young children is limited, the dosages recommended for them are conservative.

SIDE EFFECTS AND ADVERSE REACTIONS

Side effects of influenza vaccine occur infrequently. Three types of responses to influenza vaccines have been described:

1. Fever, malaise, myalgia, and other systemic symptoms of toxicity starting 6-12 hours after vaccination and persisting 1-2 days. These responses to influenza vaccine are usually attributed to characteristics of the influenza virus itself (even though it is inactivated) and constitute most of the side effects of influenza vaccination. Such effects occur most frequently in children and others who have had no experience with influenza viruses comparable to the vaccine antigen(s).
2. Immediate—presumably allergic—responses, such as flare and wheal or various respiratory expressions of hypersensitivity. These reactions are exceedingly uncommon but can occur after influenza vaccination. They probably derive from exquisite sensitivity to some vaccine component, most likely residual egg protein. Although current influenza vaccines contain only a minute quantity of egg protein, they can, on rare occasions, provoke hypersensitivity reactions. Individuals with known or suspected hypersensitivity to eggs should be given influenza vaccine only under the care and close observation of a physician.
3. Guillain-Barré syndrome, usually a self-limited paralysis, is observed within 8 weeks after influenza vaccination in approximately 10 of every million persons vaccinated. It also occurs, but less frequently, in unvaccinated persons. Prior to the intensive surveillance of influenza vaccine that occurred during the swine influenza vaccination program in 1976, serious adverse reactions, such as this syndrome, to influenza vaccines had been virtually unrecognized. While the risk is not high, persons who receive influenza vaccine should be aware of it and should recognize that 5-10% of persons with the Guillain-Barré syndrome have residual weakness to some degree and approximately 5% of them die.

PREGNANCY

Elevated rates of maternal and fetal mortality and of congenital anomalies and other fetal effects resulting from influenza infection during pregnancy have been widely discussed. Numerous reports from the 1918-19 influenza pandemic and a few small but better controlled studies in 1957-58, when the Asian influenza pandemic occurred, suggested that influenza can cause increased maternal and fetal deaths. However, a number of more recent, prospective studies have failed to corroborate those findings. Thus, although there are no persuasive data to document that pregnancy is a risk-factor with influenza, the effect of influenza in pregnancy cannot be forecast with assurance. Physicians generally avoid prescribing unnecessary drugs and biologics for pregnant women, especially in the first trimester; however, there are no data that specifically contraindicate influenza vaccination in pregnancy.

TABLE 1. Influenza vaccine dosage by age, 1977-78

Age	Product Type	Dose Volume (ml)	Total CCA Units*	Number of Doses
18 years and older	Whole-virus or Split-virus	0.5	400	1
6-17 years	Split-virus	0.5	400	1
3-5 years	Split-virus	0.25	200	2**
6-35 months	Split-virus	0.15	120	2**

*Representing equal amounts of A/Victoria/75 and B/Hong Kong/72.
**4 weeks or more between doses; both doses essential for good protection.

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Recommendation of the Public Health Service

Advisory Committee on Immunization Practices

Influenza Vaccine

INTRODUCTION

Influenza virus infections occur every year in the United States, but they vary greatly in incidence and geographic distribution. Infections may be asymptomatic, or they may produce a spectrum of manifestations, ranging from mild upper respiratory infection to pneumonia and death. Influenza viruses A and B are responsible for only a portion of all respiratory disease. However, they are unique in their ability to cause periodic widespread outbreaks of febrile respiratory disease in both adults and children. Influenza epidemics are frequently associated with deaths in excess of the number normally expected. During the period from 1968 to 1978, more than 150,000 excess deaths are estimated to have occurred during epidemics of influenza A in the United States.

Efforts to prevent or control influenza in the United States have been aimed at protecting those at greatest risk of serious illness or death. Observations during influenza epidemics have indicated that influenza-related deaths occur primarily among chronically ill adults and children and in older persons, especially those over age 65. Therefore, annual vaccination is recommended for these "high-risk" individuals.

Influenza A viruses can be classified into subtypes on the basis of 2 antigens: hemagglutinin (H) and neuraminidase (N). Four types of hemagglutinin (H0-H3) and 2 types of neuraminidase (N1-N2) are recognized among viruses causing widespread disease among humans. Immunity to these antigens reduces the likelihood of infection and reduces the severity of disease in infected persons. However, there may be sufficient antigenic variation within the same subtype over time (antigenic drift) that infection or immunization with 1 strain may not induce immunity to distantly related strains. As a consequence, the antigenic composition of the most current strains is considered in selecting the virus strain(s) to be included in the vaccine.

During 1977-78, 2 H3N2 variants, A/Victoria/75 and A/Texas/77, both related to the 1968 Hong Kong strain of influenza A, were prevalent in the United States. In 1977 a major antigenic variant, A/USSR/77 (H1N1), appeared in China and Russia. This strain is unrelated to the H3N2 strain but is closely related to strains that had circulated throughout the world in the early 1950s. From January through April 1978, the H1N1 virus spread throughout the United States, causing outbreaks in several schools and colleges, and, to a lesser extent, in young persons in the general community. Persons born more than 25 years ago were not affected, presumably because of previous infection with antigenically related strains.

In this country and elsewhere throughout the world, H1N1 strains circulated concurrently with A/Victoria/75 and A/Texas/77-like H3N2 strains. Whether or not the H1N1 strains will replace the H3N2 strains remains uncertain. However, based on present information, continued co-circulation of strains related to A/Texas/77 (H3N2) and A/USSR/77 (H1N1) must be anticipated.

Outbreaks caused by influenza B viruses occur less frequently than influenza A epidemics, but influenza B infection can also cause serious illness or death. Influenza B viruses have shown much more antigenic stability than influenza A viruses. Strains of influenza B that were isolated in 1978 in the United States and elsewhere resembled the B/Hong Kong/5/72 virus.

INFLUENZA VIRUS VACCINE FOR 1978-79

The Public Health Service reviews influenza vaccine formulation regularly, recommending changes, when necessary, to counter major antigenic changes and antigenic drift. Influenza vaccine for 1978-79 will consist of inactivated trivalent preparations of antigens representative of influenza viruses expected to be prevalent: A/USSR/77

(H1N1), A/Texas/77 (H3N2), and B/Hong Kong/72. Two alternative vaccine formulations* will be available for different age groups. The formulation recommended for individuals 26 years and older, most of whom have had prior experience with all 3 viruses, will contain 7 μg of hemagglutinin of each antigen. Only 1 dose is required for members of this age group. In contrast, the formulation recommended for persons less than 26 years of age, most of whom lack contact with H1N1 strains, will contain 20 μg of the A/USSR antigen and 7 μg each of the other 2 antigens. Persons in this age group will require 2 doses for satisfactory immunization. Both formulations will be available as "whole-virus" and "split-virus" preparations. Based on past data, split-virus vaccines have been associated with somewhat fewer side effects than whole-virus vaccines in children. Thus, only split-virus vaccines are recommended for persons less than 13 years of age.

VACCINE USAGE

General Recommendations

Annual vaccination is strongly recommended for all individuals at increased risk of adverse consequences from infections of the lower respiratory tract. Conditions predisposing to such risk include: (1) acquired or congenital heart disease associated with altered circulatory dynamics, actual or potential (for example, mitral stenosis, congestive heart failure, or pulmonary vascular overload); (2) any chronic disorder with compromised pulmonary function, such as chronic obstructive pulmonary disease, bronchiectasis, tuberculosis, severe asthma, cystic fibrosis, neuromuscular and orthopedic disorders with impaired ventilation, and residual pulmonary dysplasia following the neonatal respiratory distress syndrome; (3) chronic renal disease with azotemia or the nephrotic syndrome; (4) diabetes mellitus and other metabolic diseases with increased susceptibility to infection; (5) chronic, severe anemia, such as sickle cell disease; and (6) conditions which compromise the immune mechanism, including certain malignancies and immunosuppressive therapy.

Vaccination is also recommended for older persons, particularly those over age 65, because excess mortality in influenza outbreaks occurs in this age group.

In considering vaccination of persons who provide essential community services or who may be at increased risk of exposure, such as medical care personnel, the inherent benefits, risks, and cost of vaccination should be taken into account.

Table 1 summarizes vaccine and dosage recommendations by age group for 1978-79. These recommendations are derived from observations made during the field trials of influenza vaccines conducted in 1978.

TABLE 1. Influenza vaccine dosage, by age, 1978-79

Vaccine formulation	Age (years)	Product type	Dosage (ml)	Number of doses
Adult*	≥ 26	whole virus split-virus	0.5	1
Youth**	13-25	whole-virus or split-virus	0.5	2†
	< 13	N/A††	N/A††	N/A††

*Contains 7 μg each of A/USSR/77, A/Texas/77, B/Hong Kong/72 hemagglutinin antigens

**Contains 20 μg A/USSR/77 and 7 μg each of A/Texas/77 and B/Hong Kong/72 hemagglutinin antigens

†4 weeks or more between doses; both doses essential for good protection

††N/A - not available; final recommendations for those < 13 years old will be made in approximately 1 month

SIDE EFFECTS AND ADVERSE REACTIONS

Influenza Virus Vaccine for 1978-79 has been associated with few side effects. Local reactions, consisting of redness and induration at the site of injection lasting 1 or 2 days, have been observed in less than one-third of vaccinees. Three types of systemic reactions to influenza vaccines have been described.

1. Fever, malaise, myalgia, and other systemic symptoms of toxicity, although infrequent, occur more often in children and others who have had no experience with influenza viruses containing the vaccine antigen(s). These reactions, which begin 6-12 hours after vaccination and persist 1-2 days, are usually attributed to the influenza virus itself (even though it is inactivated) and constitute most of the side effects of influenza vaccination.

*Official names: Influenza Virus Vaccine, Trivalent, Adult Formula and Influenza Virus Vaccine, Trivalent, Youth Formula

2. Immediate—presumable allergic—responses, such as flare and wheal or various respiratory expressions of hypersensitivity occur extremely rarely after influenza vaccination. They probably derive from sensitivity to some vaccine component, most likely residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, on rare occasions they can provoke hypersensitivity reactions. Individuals with anaphylactic hypersensitivity to eggs should not be given influenza vaccine. This would include persons who, upon ingestion of eggs, develop swelling of the lips or tongue or who experience acute respiratory distress or collapse.

3. Guillain-Barré syndrome (GBS) is an uncommon illness characterized by ascending paralysis which is usually self-limited and reversible. However, 5-10% of persons with GBS have residual weakness, and approximately 5% of cases are fatal. Before 1976, no association of GBS with influenza vaccination was recognized. However, that year GBS appeared in excess frequency among persons who had received swine influenza vaccine. For the 10 weeks following vaccination the excess risk was found to be approximately 10 cases of GBS for every million persons vaccinated. The overall incidence in that period was 5-6 times higher than that in unvaccinated persons. Younger persons (under 25 years) had a lower relative risk than others and also had a lower case-fatality rate. Although there is no comparable information about the association of GBS with other influenza vaccines, it must be assumed that this risk may be present for all of them. Even though the risk (in 1976) was extremely low, persons who receive influenza vaccine should be aware of it and should balance this risk against the risk of influenza and its complications.

USE IN PREGNANCY

Although the issue has been much discussed, only in the pandemics of 1918-19 and 1957-58 has strong evidence appeared relating influenza infections with increased maternal mortality. Although several studies have reported an increased risk of congenital malformations and childhood leukemia among children born to women who had influenza infection during pregnancy, other studies have not shown an increased risk; the issue is not settled.

Physicians prudently limit prescription of drugs and biologics for pregnant women. However, no evidence has been presented to suggest that influenza vaccination of pregnant women poses any special maternal or fetal risk. Furthermore, because influenza vaccine is an inactivated viral preparation, it does not share the theoretical risks that impel caution in the use of live virus vaccines. Taking the above uncertainties into account, physicians should evaluate pregnant women for influenza immunization according to the same chronic illness criteria applied to other persons. (See **General Recommendations**, p. 291).

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